SURGICAL OUTCOMES IN ADVANCED HYPOPHARYNGEAL CANCER FOLLOWING TOTAL LARYNGOPHARYNGOESOPHAGECTOMY AND GASTRIC TUBE RECONSTRUCTION

This dissertation is submitted to

THE TAMILNADU

Dr. MGR MEDICAL UNIVERSITY

In partial fulfilment of the requirements for

M Ch (BRANCH VII)

SURGICAL ONCOLOGY

Degree Examination, 2009

COLLEGE OF ONCOLOGICAL SCIENCES

CANCER INSTITUTE (WIA)

ADYAR

CHENNAI – 600020

FEBRURARY 2009

CERTIFICATE

I hereby certify that this dissertation on "*Surgical outcomes in Advanced hypopharyngeal cancer following Total Laryngopharyngoesophagectomy and Gastric tube reconstruction*" is a bonafide work done by **DR. JADUNATH BURAGOHAIN**, in the department of Surgical Oncology, College of Oncological sciences, Cancer Institute (WIA), Chennai, under my guidance and supervision, to my satisfaction.

Dr. E. HEMANTH RAJ M Ch. PhD.

Professor and Chairman

Division of Surgical Oncology

Cancer Institute (WIA),

Adyar, Chennai – 20.

Chennai

Date : 26/11/07

ACKNOWLEDGEMENT

I express my sincere thanks and deepest sense of gratitude to our Professor and Chairman, Division of Surgical Oncology, Dr E Hemanth Raj M Ch PhD, for his scholarly guidance, masterly supervision, and encouragement in completing this project. I shall remain ever grateful to my teacher Dr Arvind Krishnamurthy

M Ch, Associate Professor, department of Surgical Oncology, for giving me kind valuable support and guidance, which has enabled me to complete my thesis work.

I express my sincere gratitude to my respected teachers Prof. Dr V Sridevi M Ch, Dr Satheesan M Ch, Dr N Kathiresan M Ch and Dr A S Ramakrishnan M Ch for their valuable advice and suggestion which helped me immensely to complete my thesis work.

I sincerely acknowledge the help of my fellow post graduate students.

I express my deepest sense of gratitude and respect from the core of my heart to the leaders in the realm of oncology in India, **Dr. Krishnamurthy**, Advisor and **Dr. V Shantha**, Executive Chairman, Cancer Institute (WIA).

The task would have been indeed more difficult without the help of the staff at the tumor Registry and Epidemiology Division at the Cancer Institute (WIA) specifically **Mr. Shivakumar** for his help.

Last but not the least, I thank all my patients for their kind co-operation in this study

Lastly I acknowledge the role of Almighty in giving me the strength and courage in completing this thesis work.

CONTENTS

INTRODUCTION

Hypopharyngeal carcinoma is associated with the highest mortality of all cancers of the head and neck. Poor survival rates are attributed to a preponderance of late presentations and to the unique behaviour of tumors occurring in this location. Tumors of this region typically remain silent until the disease has reached an advanced stage and causes symptoms from airway or digestive tract obstruction or pain from neural invasion. These are usually aggressive in behaviour, grow in an area of abundant lymphatic drainage, fail to produce early symptoms and signs and usually occur in people who are depleted nutritionally and immunologically compromised and hence treatment is difficult. Squamous cell carcinoma (SCC) accounts for 95% of hypopharyngeal pathology. It is one of the leading cause of cancer related morbidity and mortality in our country. Incidence of head neck cancer in India according to National Cancer Registry (2004-2005) 16.4 per 100,000 in males and in females 6.7 per 100,000 and hypopharyngeal cancer constitute 2.4 and 0.8 per 100,000 males and females respectively. Incidence of head neck cancer according to Madras Metropolitan Tumor Registry (MMTR 2003 -2005) 22.1 and 9.3 per 100,000 males and females respectively and hypopharyngeal cancer incidence is 3.7 and 1.6 per 100,000 males and females respectively and Hypopharyngeal cancer constitute 5.3% and 2% of all cancers in males and females respectively in our institute and around 100 cases of hypopharyngeal cancers are registered every year in our institute. More than 70% of these cases present with advanced stages III and IV.

Hypopharyngeal carcinoma is associated with a high incidence of submucosal spread,

which can be difficult to detect clinically and can result in underestimating the extent of disease. Cervical metastases are present in 60-80% of patients who have hypopharyngeal tumors have stage III or IV. They are less amenable to definite treatment by surgery and/or radiotherapy. Locoregional control with surgery or radiotherapy alone is extremely poor. The overall 5-year disease-specific survival rate is approximately 30% to 35%[1] using multimodality approach. Despite increasing use of laryngeal preserving protocols, Total laryngopharyngoesophagectomy (TLPO) remains the gold standard treatment for locally advanced hypopharyngeal and upper oesophageal cancers. Nevertheless, recent advances in reconstructive techniques and perioperative care have allowed TLPO for advanced disease with single-stage reconstruction with gastric pull-up for a functional alimentary tract. In addition, improved locoregional control has been demonstrated with the use of combined-modality therapy. Overall survival rates remain poor and largely unaffected, however, because of a shift in the pattern of failure from local to distant disease and the development of second primary tumors. Therefore, treatment goals are aimed at eradicating disease and restoration of function, while causing the least morbidity and the most effective palliation of symptoms.

Surgical ablation of advanced tumors of the hypopharyngeal and upper esophageal regions, together with optimal reconstruction of the resultant defect, has remained a surgical challenge. The goal of this surgery is a single stage reconstruction with low morbidity and mortality, short hospital stay, and early restoration of swallowing.

ANATOMY OF HYPOPHARYNX:

The hypopharynx, or laryngopharynx, is interposed between the oropharynx and the esophagus. It extends from the level of the hyoid bone or from the level of the pharyngoepiglottic fold down to the upper esophageal sphincter which corresponds approximately to the sixth cervical vertebrae or the lower border of the cricoid cartilage. It is bordered anteriorly by the larynx and posteriorly by the retropharyngeal space. It is subdivided into three regions: the pyriform sinuses, the post-cricoid region, and the posterior pharyngeal wall.

The pyriform sinuses are pyramidal shaped areas with the base situated superiorly and the apex inferiorly. The superior extent is the oropharynx and pharyngoepiglotic folds. It is divided into a superior or membranous part and inferior or cartilaginous part. The superior aspect of the pyriform sinus bounded laterally by the thyrohyoid membrane, through which passes the internal branch of superior laryngeal nerve. The lower portion bounded anterolaterally by the medial surface of the thyroid cartilage and the anteromedially by the lateral surface of the cricoid/arytenoid cartilages. The sinuses are bounded posteriorly by the lateral and posterior pharyngeal walls.

The post-cricoid area is the posterior surface of the arytenoid and cricoid cartilages. It terminates inferiorly at the pharyngoesophageal junction and is intimately related to the apex of each pyriform sinus laterally.

The posterior pharyngeal wall extends from a level of the hyoid bone to the level at the lower extent of the cricoid cartilage. It meets the posterior oropharyngeal wall superiorly

and meets the posterior wall of the esophagus inferiorly. It is related posteriorly to the retropharyngeal space.

The hypopharyngeal wall is made up of mucosa, pharyngobasilar fascia, constrictor musculature, buccopharyngeal fascia (in a lumen to external direction).

The mucosa is stratified squamous epithelium. The pharyngobasilar fascia is more developed in the nasopharynx and is less so as it approaches the hypophayrnx. External to the pharyngobasilar fascia is the musculature composed of the middle and inferior constrictors.

The constrictors are innervated by the laryngeal nerves as well as the pharyngeal plexus. The middle constrictor takes its origin from the lesser/greater cornu of the hyoid bone and the inferior constrictor originates from the oblique line of the thyroid cartilage as they both insert into the midline pharyngeal raphe. The lower fibers of the inferior constrictors blend into the cricopharyngeus muscle.

The buccopharyngeal fascia is a thin layer covering the external aspect of the constrictor muscles. There are gaps between the constrictors as they overlap one another.

The glossopharyngeal nerve, styloid ligament, stylopharyngeus muscle, and the lingual artery traverse the gap between the superior and middle constrictor muscles. The area between the middle and inferior constrictors is not a true gap since the thyrohyoid membrane closes this area. However, the superior laryngeal artery and vein, as well as the internal laryngeal nerve traverse this area. The inferior laryngeal artery and vein and the recurrent laryngeal nerve traverse the space between the inferior constrictor and the esophagus.

LYMPHATIC DRAINAGE OF HYPOPHARYNX

Lymphatic drainage of the hypopharynx is extensive. The pyriform sinuses are drained by a network of lymphatics, which drain primarily to the upper and middle jugular nodes, posterior cervical nodes, and retropharyngeal lymph nodes. Lymphatics of the posterior wall of the hypopharynx drain to the jugular nodes and retropharyngeal nodes. Postcricoid lymphatics drain to the middle and lower jugular nodes and to the paratracheal nodes (Million, 1994). Between 60% and 75% of patients will have clinically involved neck nodes (node positive) at presentation and more than one third of patients without clinically evidence of nodal disease will harbour occult metastases [3-8]. In patient with N+ disease, Level II (72%-75%), III(55%-72%), and IV (21%-45%) are most often affected; Level I (1%-10%) and V (11%-15%) are less commonly affected[9,10]. Controlateral occult nodal metastases are present in 37% of patients with N+ disease[11]. In patient who has clinically N0 tumors, 36% harbour occult nodal metastases in the ipsilateral neck, and 27% have occult disease in the contralateral neck [11.] Metastatic disease involves the retropharyngeal lymph nodes in at least 20% of patients who have hypopharyngeal cancer[12].

SPREAD

The intimate association between the hypopharynx and the larynx, oropharynx, and esophagus provide for certain dissemination routes of malignant disease. Cancer of the medial wall of pyriform sinus may spread superficially toward the lateral epilarynx (aryepiglotic fold, arytenoids). It may infiltrate deeply to the pharyngolaryngeal wall, including the cricoarytenoid joint. Involvement of pre-epiglotic and paraglotic spaces and involvement of recurrent laryngeal nerve beneath the mucosa of pyriform sinus may lead to

fixation of hemilarynx. Tumors of the lateral wall spread rapidly to the ala of the thyroid cartilage and thereafter the ipsilateral thyroid lobe.

Cancer of the postcricoid region frequently invades the posterior cricoarytenoids muscles and the cricoid and arytenoids cartilges. The apex of the pyriform sinus terminates in the postcricoid area and is often invades early. Advanced tumor may totally encircle the hyphopharyngeal lumen.

Cancer of the posterior pharyngeal wall usually manifests as ulcerating and infiltrating lesions that spread both superficially and submucosally to the entire posterior pharyngeal wall from the nasopharynx to the cervical esophagus. These lesions may spread posteriorly to the prevertebral muscles and the retropharyngeal space, but vertebral bone extension is rare. Carcinomas of posterior pharyngeal wall may spread laterally to both pyriform sinuses.

Distant metastases is rare at presentation mostly to lung, bones and liver commonly.

EPIDEMIOLOGY

The incidence of hypopharyngeal cancer is much higher in men than in women, although the incidence in women is rising as more women are smoking. The annual incidence is 1 per 100,000 persons and corresponds to 8% to 10% of head and neck malignancies. Highest incidence countries are France and India with an annual incidence ranging between 8 and 15 per100,000 men.[25.] These cancers usually occur during the second half of life, with a peak incidence in fifth and sixth decades. The increase incidence of hypopharyngeal cancer is closely associated with lower socioeconomic classes and lower level of education.

1. More common in Western India and Far East. But all races are affected (David Wight

1970) often seen in fifth and sixth decade.

2. Males are commonly affected because of habits of smoking, pan and tobacco chewing but rare in females (J D baruah 1980, SC Pandi 1974 John A Keichner 1975)

PRE DISPOSING FACTORS:

Tobacco and ethanol are the principle carcinogens responsible. Long-term exposure causes progressive cellular dysregulation by alteration of tumor suppressor genes such as *TP53,* amplification of proto-oncogenes such as cyclin D1, and damage to regulatory factors such as transforming growth factor–beta (TGFβ) and retinoic acid receptors. The progression from normal mucosa to cancer correlates with accumulation of genetic abnormalities. Genetic factors are under investigation. Heritable polymorphisms of expression of enzymes that activate tobacco-related procarcinogens (eg, aryl hydrocarbon hydroxylase) and detoxify carcinogens (eg, glutathione S-transferase) have been identified. Certain polymorphisms in the alcohol dehydrogenase genes may increase the risk of oral and pharyngeal cancers related to alcohol consumption. Racial differences in the metabolism of carcinogens may be a possible cause of the increasing incidence in African Americans. Deficient DNA repair mechanisms increase susceptibility to head, neck, and other cancers. Clinically recognized syndromes include xeroderma pigmentosum, Bloom syndrome, ataxia-telangiectasia, and Fanconi anemia.

Irritation: Hypopharynge cancer is definitely linked to the excessive use of

both tobacco and alcohol, which are generally the prime etiologic factors for squamous cell carcinoma of the upper aerodigestive tract. Long standing irritation due to smoking, tobacco chewing, alcoholism and nutritional deficiencies leads to hyperkeratosis, dyskeratosis,

leokoplakia and finally malignancy.

The Plummer-Vinson or Paterson-Brown Kelly syndrome represents a

combination of dysphagia, postcricoid web, weight loss, and iron deficiency anaemia, usually occurring in non-smoking women between the ages of 30 and 50 years. Patients with this syndrome are at higher risk of developing cancer of the hypopharynx, particularly in postcricoid region.

The role of human papilloma virus (HPV) in cancers of the hypopharynx is unclear, although it may play more of a role in cancers of the oropharynx and oral cavity. Epidemiologic and molecular biology studies have suggested that HPV infection may be associated with cancers of the head and neck. Based upon the most sensitive method of detection, polymerase chain reaction (PCR), the overall prevalence of HPV in head and neck tumors was 20% to 34.5% (416 of 1205 tumors) [[90,91]. Among head and neck sites, HPV was most often detected in tumors of the oral cavity (59%), followed by the pharynx (43%), and larynx (33%).

CLINICAL FEATURES

Sore throat, sensation of foreign body and then mucus retention that felt only on swallowing are the commonest symptoms. More than 50%-70% patients present with clinically obvious cervical nodes and in half of these the neck mass is the presenting symptoms. Voice change is a late symptom and usually due to impairment of vocal cord function by invasion into endolarynx or of recurrent laryngeal nerve. Weight loss, because patient has lost their ability to swallow comfortable or have lack of willingness to swallow because of fear of aspiration. Dysphagia due to tumor invasion often causes a combination of painful

swallowing (odynophagia) and neuromuscular dysfunction (dysphagia) and most commonly large circumferential tumour which completely occlude the lumen. Otalgia, referred pain to the ear is mediated by branches of the tenth cranial nerve. Invasion of the laryngeal nerve causes spread of neuropathic impulses to the auricular nerve (Arnold's nerve, sensory to posterior external auditory canal and back of pinna). Fetid breath, halitosis is due to saprophytic bacterial overgrowth in fungating necrotic tumors.

PHYSICAL EXAMINATION

Performance status to assess the general health condition whether he/she will withstand a particular treatment procedure. Most of the patient of hypopharyngeal cancer patient will be nutritionally poor and they may require nutritional support before definitive procedure. Neck examination which includes examination and documentation the size, location, and number of palpable lymph nodes in all cervical and supraclavicular node-bearing areas. Documentation of laryngeal expansion if present. Assessment thyro-vertebral crackle. Tenderness suggests invasion of prevertebral muscles excludes curative treatment options, while loss of normal thyrovertebral crepitus suggests invasion of prevertebral tissue or a large postcricoid tumor. Assessment of extrapharyngeal extension of disease and involvement of thyroid gland. Examination of oral cavity under good light to exclude other regional pathologies, including the synchronous oral cavity or oropharyngeal tumors, might be seen. Lesion extending to posterior pharyngeal wall of oropharynx can be seen directly. The Indirect laryngoscopic examination to know the site and extension of disease, but it cannot reveal lower pyriform sinus or postcricoid lesions. Fiberoptic laryngoscopy is the examination of choice. Findings include mass lesions, hyperkeratotic or erythematous

mucosal lesions, ulcerations, and vocal cord paralysis. General examination and systemic examination to exclude distant metastases and for comorbidities as patient has to withstand major surgical procedure.

LAB STUDIES

- Routine Hematological examination and Blood Biochemistry

- Prothrombin time (PT) and activated partial thromboplastin time (aPTT): These are used to assess the safety surgical procedures.

IMAGING STUDIES

- Chest x-ray films to check for lung metastases, synchronous lung cancer, and comorbid heart or lung disease.

- CT scan Head and neck - Evaluate local extent of tumor and cervical nodes, and very rarely MRI of head and neck to assess the extension of disease. Other Tests as required by anaesthetist for assessment for fitness for major surgery

PROCEDURES

- Biopsy - To confirm diagnosis and usually is performed during a Flexible fiberoptic Direct laryngoscopy and Direct pharyngoscopy (DLDP) & UGI endoscopy.

DLDP & UGI endoscopy.

This operating room procedure, performed by a surgeon, is an essential step in planning the definitive treatment for all head and neck subsites. With rigid direct larygoscopy under general anaesthesia the extent of the tumor can most accurately be ascertained & mostly when there is doubt about the extension of disease in fiberoptic flexible endoscopy. Post cricoid region and involvement of pyriform sinus can be accurately assessed in rigid DL.

Biopsies of all suspicious lesions are taken. Esophagoscopy are performed to rule out synchronous cancers and for assessment of stomach tube if scope can be introduced beyond the lesion.

HISTOPATHOLOGY IN HYPOPHARYNGEAL CANCER

More than 95% of hypopharyngeal tumors are squamous cell carcinoma, less than 60% are keratinizing, 33% are nonkeratinizing, and all are usually poorly differentiated. Variants include basaloid squamous cell carcinoma, superficial spreading cancer, sebaceous cancer, adenosquamous cancer, and signet-ring and verrucous types. Uncommon histologic types include adenocarcinoma, lymphoma, and sarcoma.

Studies have reported that tumor margins are usually infiltrating (80%) but can be pushing (20%). Skip lesions or multifocal areas of disease are not unusual. Histologic factors that denote a higher risk tumor include lymphovascular invasion, perineural invasion, or poorly differentiated cell morphology.

Natural history of hypopharyngeal squamous cell carcinomas

In general, 30% of patients have local disease at the time of diagnosis, 60-70% have local regional disease, and 6% present with distant metastases [37]. In the United States, most hypopharyngeal tumors (60-70%) arise in the pyriform sinus, 25% are found in the posterior pharyngeal wall, and 5% are found in the posterior cricoid region. Most patients present with large T3 or T4 tumors. Medial wall pyriform sinus tumors usually spread along the mucosal surface to the aryepiglottic folds and can invade into the larynx by involving the paraglottic space. Tumors of the lateral wall and apex commonly invade the thyroid cartilage. Once the tumor penetrates the constrictor muscle, it can spread along the fascial

planes to the base of skull.

Because of the abundant lymphatics in the region and the extent of the primary tumor at diagnosis, metastasis to the regional lymph nodes is common.

The location of the lymph node metastasis is an important consideration in the treatment of hypopharyngeal cancers. In necks that are clinically negative, the lymphatic drainage is to the cervical nodal groups, with level II and III nodal regions typically involved. In necks that are clinically positive, not only is the risk of occult contralateral neck metastasis increased, but the risk of involvement of level I and V must also be considered because the risk is approximately 10% for these sites. This is likely due to an alteration in the lymphatic flow pattern found in clinically involved nodes, typically in the level II and III regions of the anterior cervical neck. The increased risk of retropharyngeal lymph node metastasis in patients with cervical lymph node metastasis is more significant (as high as 90%) when compared with patients without cervical lymph node metastasis.

This altered lymphatic spread pattern is also influenced by the location of the cancer within the hypopharynx. For cancers that involve the pharyngeal wall, as opposed to the pyriform sinus, the risk of level I and V nodal metastasis appears to be as high as 20%.

Patients with cancers of the hypopharynx, particularly cancers that involve the postcricoid region (with or without extension into the cervical esophagus) are also at an increased risk of paratracheal lymph node metastasis. This risk may be as high as 35% and increases in the presence of cervical nodal metastasis. Treatment for these cancers should be considered in patients with mucosal involvement of the postcricoid region, with or without extension into the cervical esophagus.

Eight to 26% of patients present with a second primary tumor that is either synchronous (current) or metachronous (sequential). The secondary malignancies usually occur in the oropharynx, lung, and esophagus. Synchronous primary tumors are rare (7.4%). Metachronous lesions are more common and can occur at a rate of 2 to 4% per year. Overall, some series report second primary tumors as a cause of death in 16% of patients.

GENERAL PRINCIPLES OF TREATMENT

Currently, several treatment options exist for patients who have hypopharyngeal cancer. Surgery combind with radiation therapy is the standard treatment for most patients who have hypopharyngeal carcinoma. Radiation therapy alone also may be used and seems to be most useful for small (T1 or T2) lesions. Hyperfractionated radiation therapy seems to confer some advantages over conventional radiation therapy in improved locoregional control. Organ preservation therapy using chemoradiation is being increasingly studied and may result in larynx preservation in one third of patients. Cetuximab, a monoclonal antibody against the epidermal growth factor receptor, plus radiotherapy for locoregionally advanced squamous-cell carcinoma of the head and neck has emerging but the use of this antibody did not improve the survival among patients with hypopharyngeal cancer [14].

SURGICAL TREATMENT

Preoperative evaluation is critical including age and general condition and presence of intercurrent of illness of the patient in determining the appropriate surgical approach for treatment of hypopharyngeal carcinoma. The location and extent of disease determine the extent of resection required. Accurate staging is necessary to assess the defect whether a partial or circumferential hypopharyngeal defect after resection and total laryngectomy is required or not and to know the extent of neck dissection.

The predilection of hypopharyngeal carcinoma for submucosal spread must be kept in mind when planning resection of the primary tumor. Wei[15] suggested that based on measurement of submucosal extension in whole organ studies, an adequate resection margin in patients who have not received previous radiation therapy is 15mm superiorly, 30mm inferiorly, and 20mm laterally. Patients who have undergone previous radiation therapy require resection margin of 20mm superiorly, 40mm inferiorly, and 30mm laterally. The deeper margin in either situation should be greater than 1mm to ensure complete removal of the tumor without leaving residual disease in the prevertebral musculature [15].

TOTAL LARYNGOPHARYNGOESOPHAGECTOMY (TLPO)

TPLO is indicated in the following instances[16]:-

1. Annular postcricoid carcinoma

2. Extensive lesions of the pyriform sinuses with involvement of more than two thirds of the circumference of the hypopharynx.

3. Extensive posterior pharyngeal wall lesions with involvement of the larynx

4. Carcinoma of the cervical esophagus.

5. Carcinoma of hypopharynx that involves the apex of the pyriform sinus. The proximity of the apex of the pyriform to the postcricoid mucosa requires total laryngectomy and cervical esophagectomy in addition to partial pharyngectomy for removal of the tumor and results in a circumferential pharyngeal defect [3].

REVIEW OF LITERATURE

Currently, several treatment options exist for patients who have hypopharyngeal cancer. Surgery combined with radiation therapy is the standard treatment for most patients who have hypopharyngeal carcinoma.

PRIMARY RADIATION THERAPY

The results of treatment with primary radiation therapy for curing patients who have hypopharyngeal cancer are not so favourable. Local control rates early-stage disease have been reported to range from 77% to 89%, with 5 year disease-specific survival rates as high as 69% [3, 37, 59]. Advanced-stage primary disease (T3 and T4) and advanced-stage nodal disease (N2 and N3) are associated with dismal rates of laryngeal preservation and 5 year disease-specific survival rates of 0 to 12%. Surgical salvage after failure of radiation therapy is successful in less than 10% of patients, and larynx preservation is rarely possible [60, 61]. Fewer than one third of patients are alive at 5 years with a functional larynx[62].

Several nonrandomized studies reported that hyperfractionated radiation therapy provides a 15% to 25% improvement in local control rates for larger tumors.[89.] There is an increased incidence of treatment-related complications in hyperfractionated radiation therapy when compared to conventional radiotherapy and these complications are dose related. Hyperfrationated radiation therapy seems to improve local control rates but incurs socioeconomic and time constraints and does not seem to result in improved survival when compared to conventional radiation therapy. [89]

CHEMOTHERAPY

For a long-time chemotherapy was used primarily for palliative purpose only because of poor activity in Head and Neck cancer. A new era in the management of cancer of Head and Neck was initiated in the early 1980s with the introduction of platinum-based chemotherapeutic regimens. Clinical studies using cisplatin as a single agent or more often in combination with other drugs have demonstrated partial response rates of 40 to 50%, and complete response rates of 20% to 30%, for an overall response rate ranging between 78% and 94%. [65, 66.] In the early 1990s, it appeared obvious that use of chemotherapy had not provided any improvement in survival benefit for most patients. The major meta-analysis carried out at the Institut Gustave Roussy (Meta-analysis of Chemotherapy in Head and Neck Cancer [MACH-NC][67] which included more than 10,000 patients enrolled in randomized trials comparing conventional treatment with the same treatment combined with chemotherapy (adjuvant or induction or concomitant). The conclusion of this meta-analysis was that adjuvant chemotherapy, as well as induction chemotherapy (4%), produced a nonsignificant increase in survival (1%). Concomitant chemoradiotherapy resulted in a significant increase in survival of 8%, but this group had a mixture of definitive and postoperative radiation trials.

CHEMORADIOTHERAPY

Patients who respond to chemotherapy show a subsequent response to definitive radiation therapy, suggesting that tumors that are sensitive to chemotherapy are radiosensitive. In 1990, the use of chemoradiation for organ preservation was established by Department of veterans Affairs Laryngeal Cancer Study Group in a landmark prospective randomized trial

[63]. Induction chemotherapy with cisplatin and 5-FU, followed by definitive full-course radiation therapy in responders, resulted in larynx preservation two thirds of patients who otherwise would have required total laryngectomy, without compromising survival.

The only randomized, prospective phase 3 trial to date investigating chemoradiation in patients who have hypopharyngeal cancer was conducted by the EORTC Head and Neck Cancer Cooperative Group [64.] Patients with T2 to T4 lesions who required total laryngectomy as part of definitive surgical treatment were randomized to receive either induction chemotherapy with cisplatin and 5-FU followed by definitive radiation therapy, or to surgery with postoperative radiation therapy. This trial found no significant difference between the chemoradiation arm and surgery arm in local (12% and 17%, respectively) or regional (19% and 23%) recurrences rates and 5 year disease free survival rates. A decreased incidence of distant metastases was identified in the organ preservation group compared with the surgery group (25% versus 36%, respectively). The 5 year estimate of retaining a larynx for the chemoradiation group was 35%.

SEQUENTIAL THERAPY

Patient treated with induction chemotherapy continue to have a high rate of locoregional treatment failure, whereas chemoradiotherapy has reduced locoregional treatment failure with no improvement in control in distant disease. This has lead to the development of sequential therapy approaches, combining induction chemotherapy, chemoradiotherapy and surgery. Recent phase III data have shown that adding a taxane to cisplatin and 5-FU induction chemotherapy results in a significant improvement in survival with less toxicity. Phase III Study by Hitt et al[67] induction taxane with cisplatin and 5-FU(TPF) have followed

by cisplatin based chemoradiotherapy(CTRT) versus induction with cisplatin and 5-FU (PF) followed by cisplatin based CTRT in resectable and unresectable Head and Neck cancer patients have shown improvement in response and in overall survival in patient treated with TPF. Complete response rate was 33 % and 14 % for TPF and PF respectively. Toxicity with TPF arm was less than that of PF arm. Second phase III trial by Vermorken et al.[68] patients with unresectable disease were treated with Docetaxel-based cisplatin and 5-FU (TPF) or cisplatin and 5-FU, followed by radiotherapy. Survival in TPF arm was significantly superior to that obtained in cisplatin and 5-FU arm and toxicity was better with TPF compared to cisplatin and 5-FU [68.] Although sequential therapy makes sound biological sense and seems to be highly effective, it still remains experimental.

MONOCLONAL ANTIBODY IN HYPOPHARYNGEAL CANCER :

The epidermal growth factor receptor (EGFR), a member of the ErbB family of receptor tyrosine kinases, is abnormally activated in epithelial cancers, including head and neck cancer.[69, 70..] The cells of almost all such neoplasm express high levels of EGFR, a feature associated with a poor clinical outcome.[69, 71-76] . Radiation increases the expression of EGFR in cancer cells, and blockade of EGFR signaling sensitizes cells to the effects of radiation.[77,78]

Cetuximab, an IgG1 monoclonal antibody against the ligand binding domain of EGFR, enhances the cytotoxic effects of radiation in squamous-cell carcinoma [79-83]. Cetuximab as a single agent or combined with cisplatin was also associated with clinically significant rates of tumor regression in patients with platinum-refractory head and neck cancer.[85, 86] Bonner et al.[87] report on the phase 3 study of cetuximab, a monoclonal antibody against the

epidermal growth factor receptor, plus radiotherapy for locoregionally advanced squamous-cell carcinoma of the head and neck. Bonner et al. found an improvement in locoregional control, progression-free survival, and overall survival among patients treated with cetuximab plus radiotherapy, as compared with radiotherapy alone. Furthermore, the addition of cetuximab did not increase the incidence of severe mucositis. However, Bonner et al. did not compare the combination of cetuximab plus radiotherapy with the current standard of care — platinum-based chemoradiotherapy and they did not administer the radiotherapy uniformly among all patients. These caveats complicate the interpretation of the study's results. In this cetuximab appeared to be effective only when added to hyperfractionated radiotherapy. In subset analysis there was no benefit in hypopharyngeal cancer. The long-term, absolute improvement has yet to be determined, however, and adding cetuximab had no effect on distant metastases. Moreover, the benefit from adding cetuximab to radiotherapy may be specific to particular sites of head and neck cancer and to the type of radiotherapy that is administered. Whether cetuximab plus radiotherapy is a better therapy than platinum- based chemoradiotherapy and whether cetuximab can be added to platinum-based chemoradiotherapy are important questions, the answers to which require randomized phase 3 studies. These are already under way.

Treatment of advanced carcinoma of the head and neck regions remain a challenging problem to the oncologists world wide. Despite advances in surgical and nonsurgical treatment, overall survival rates for patients who have hypopharyngeal carcinoma have not improved, and the disease still has a poor prognosis. The best results are obtained with multimodality therapy, but at best, two thirds of patients are palliated rather than cured of

disease. For most patients, surgery alone does not provide sufficient disease control. Retrospective reviews comparing surgical treatment alone with surgery plus postoperative radiotherapy have shown decreased locoregional recurrence rates (11%-14% Vs 39%-57%, respectively) and improved 5 year disease-specific survival rates (40%-48% Vs 18-25%, respectively) with the addition of postoperative radiation therapy[8,13]. Radical surgery with postoperative radiation therapy remains the standard of care. Organ preservation strategies have not been as successful in hypopharyngeal cancer as for cancers of other head and neck sites. Chemoradiation is an effective alternative method of aggressive treatment but may be associated with significant dysfunction of end organ when preservation is possible. Because of poor long-term survival rates, local control remains the most important factor in planning treatment, to provide meaningful palliation and best possible quality of life.

A recapitulation of the experience of the past 50yrs with TLPO with pharyngoesophageal reconstruction demonstrates numerous instances of prolonged hospitalisation, multiple operations, and persistent salivary fistulae. Effective palliation however, is possible only if reconstruction of the pharyngoesophageal segment is accomplished rapidly and consistently. Unfortunately, this is not an easy task. All too often the tumor recurred before reconstruction of the esophagus completed.

With Pharyngoesophageal reconstruction, as with all difficult surgical problems when no single approach has offered an ideal solution, a large number of different techniques, with their inherent difficulties, have been supplanted by new procedures that have produced more consistently successful results with greater rapidly and with less morbidity than was previously feasible. The advent of free tissue transfer procedures and one-stage procedures

involving transfer of abdominal viscera has revolutionized the reconstruction of the hypopharynx and the cervical esophagus. Several feasible options are now available for reconstruction of these massive defects, all of which have good success when performed properly.

Historically, various methods of reconstruction have been used after resection of the pharynx, hypopharynx, and cervical esophagus. These have included local skin flaps; deltopectoral flaps; reversed gastric tube esophagoplasty; pectoralis major myocutaneous flaps; visceral interposition with stomach or colon; and free tissue autografts utilizing colon, jejunum, and tubed radial forearm flaps. Free jejunal transfer has become the standard technique for reconstruction of the pharynx and hypopharynx, especially with proximal lesions [3-5] whereas gastric tube interposition is the technique of choice for reconstruction of the hypopharynx and cervical esophagus when the resection extends below the thoracic inlet [6-11].

The first successful resection of the cervical esophagus was performed in 1877 by Czerny. Mikulicz reported the first successful cervical esophagus reconstruction in 1886. A variety of pharyngoesophageal reconstructive techniques have emerged between 1900 and 1995. The Cervical flaps are amongst the earliest methods of reconstruction. Wookey popularized the repair of pharyngoesophageal defects using local cervical tissues in 1942. He used laterally based cervical flaps which were partially folded back on themselves and sutured is the pharyngeal and esophageal ends to form a tube that was open laterally. The tubing of the flap was completed later and the neck defect was covered with a spilt thickness skin graft. Many modifications of this technique have been described, but the basic principle of

using anterior cervical skin to resurface the neopharynx is constant. The modifications deal with different strategies for the resurfacing the neck defect. The use of skin form the anterior chest wall for reconstruction of the pharyngoesohagus regained popularity in the 1960's with description of the deltopectoral flap by Bakamjian. This remained the standard method of reconstruction until the advent of the myocutaneous flap in the late 1970's.

The use of the pectoralis major myocutaneous flaps (PMMC) in head and neck reconstruction was first described by Aryian in 1979. Theogaraj in 1980 reported a series of pharyngoesophageal reconstruction using a tubed PMMCF. A variety of abdominal viscera have been used to reconstruct the alimentary tract after resection of the hypopharynx and cervical esophagus. Ong and Lee in 1960 reported a technique of mobilizing and anastomosing the stomach to the pharynx. Keling and Vuillet were the first to independently report on a transverse colon transposition for reconstruction of the esophagus in 1911. Huguier et al in 1970 reported the first series of free jejunal grafts for reconstruction of the cervical esophagus. Many modifications have been described in an effort to decrease mortality and morbidity but the basic techniques remain the same. The use of tubed radial forearm free flap was first reported by Harii in 1985. Reports of the use of other fasciocutaneous free flaps for reconstruction of the cervical esophagus and hypopharynx have surfaced since then.

GASTRIC TRANSPOSITION:

Replacement of the esophagus by transposition of the stomach tube through the posterior mediastinum into the neck with direct pharyngogastric anastomosis has proved to be a satisfactory procedure in selected cases. Resection of the pharynx and larynx is combined

with closed resection of the thoracic esophagus. The stomach tube is transposed through the posterior mediastinum, in the bed of the previously resected esophagus. The operation is performed in one stage, and only one anastomosis is required. The blood supply of the transposed stomach superior to that of other organs used as esophageal substitutes, and the pharyngogastric anastomosis is particularly resistant to stricture formation or leakage.

The idea of performing blunt total esophagectomy through cervical and abdominal incision was suggested by Denk[17] who in 1913 performed the procedure in cadavers and experimental animals. Turner[18], in 1936, was the first to use this approach successfully for resection of intrathoracic esophageal carcinoma. In 1960 Ongo and Lee[19] reported three cases of transposition of the stomach through posterior mediastinum for esophageal replacement after pharyngolaryngectomy. LeQuesne and Ranger[20], in 1966, reported their experience with 14 cases of gastric transposition for esophageal replacement. The first three patients had undergone a three-incision procedure with laparotomy and thoracotomy, as well as cervical dissection. Because of poor results obtained with these patients, the authors began to use the technique of closed chest blunt dissection of the normal thoracic esophagus. Elimination of the thoracotomy lessened the morbidity and mortality of the procedure a great improvement in the results. Further modifications and improvements in the procedure were subsequently reported by Stell[21], Leonard and Maran[22], Silver [23], and Akiyama et al [24].

Gastric transposition is less suitable for hypopharyngeal tumors that extend upward rather than inferiorly. This is most often encountered with posterior pharyngeal wall lesions that rarely extend below the cricopharyngeal muscle but may extend upward into the

nasopharynx. Although transposed stomach easily reaches to the level of the base of the tongue, posterior pharyngeal wall anastomosis farther superiorly would be difficult. Microvascula free flap is suitable in this situation. Gastric transposition is quite successful in heavily irradiated patients (25, 26) and is preferred in these instances.

Occasionally, gastric transposition is technically impossible. A gastroduodenal ulcer or a tumor or scarring and tissue loss from previous gastric surgery may preclude the use of the stomach for esophageal replacement. The right gastric vessels and right gastroepiploic vessels must be intact, and there should be no interruption of the vascular arcades along the greater curvature to ensure an adequate blood supply of the transposed stomach. Previous thoracic, mediastinal, or upper abdominal surgery may make blunt esophagectomy without thoracotomy impossible.

RECONSTRUCTION CRITERIA

Reconstruction of a defect after resection of the hypopharynx and cervical esophagus remains one of the greatest challenges to the head and neck surgeon. The ideal reconstruction would restore normal anatomy, allow for normal deglutition without aspiration, allow for development of speech and for breathing without a tracheotomy. It is obvious that with our present skill and technology this type of reconstruction cannot be achieved. Patients with advanced cancer of hypopharynx and cervical esophagus have a very poor prognosis. Survival of these patients is approx. 50% at 1 year 20-30% at 5 years. Consequently, surgery for these patients should be considered primarily palliative, and the optimal reconstruction should preserve the quality of life for the duration of survival.

The optimal reconstruction should therefore have the following characteristic:

- Single stage reconstruction.
- Low mortality & morbidity.
- Short hospitalization.
- Short interval to successful oral alimentation
- High rate of speech development.
- Tolerate postoperative radiation. (~ 6000cGy)

RECONSTRUCTIVE OPTIONS

1) Local tissues

a) Primary closure b) Laryngeal flaps

2) Skin grafts

3) Cutaneous flaps

a) Cervical b) Deltopectoral

4) Myocutaneous flaps

a) Pectoralis major b) Latissimus dorsi

c) Trapezius

5) Visceral transposition

a) Gastric "pull-up" b) Jejunal autograft (free flaps),

c) Colonic pullup.

6) Fasciocutaneous free flaps (FCF)

a) Radial forearm b) Lateral thigh

c) Scapula d) Other

There is significant increase in mortality and serious morbidity in patients undergoing visceral transposition. The skin, myocutaneous, and free fasciocutaneous flaps patients had less mortality and morbidity, but a higher rate of stenosis and fistula formation. Single stage reconstructions are characterized by rapid alimentation (7-12 days). The myocutaneus flap patients had a longer interval to alimentation (20-60 days) due to the high rate of significant fistulae which at times required a second procedure.

Skin and muscle flaps tolerate radiation best, while the stomach tolerates it the poorest. The development of adequate speech with the aid of prosthesis after reconstruction is best achieved with the FCF followed by the cutaneous and myocutaneous flaps. The development of speech with the visceral transpositions is generally poor but is better with the gastric pull-up.

DEFECT FACTORS

The important defect factors are

1) Size: the size of the defect can be classified as follows:

a) Minor: defect less than 30% of the circumference of the pharynx or resection of maximum of 2 cm of the pharyngeal wall

b) Major: defect that is greater than 30% but less than 70% of the pharyngeal circumference or a resection that is greater than 2 cm but at least a 2 cm stripe of pharyngeal mucosa is left

c) Circumferential: defect greater than 70% of the pharyngeal circumference or a resection were less than a 2 cm stripe of mucosa is left.

2) Presence of the larynx: This can rarely be performed due to

oncologic or functional reasons

3) Inferior extent of the tumor

Pradhan SA et. al. analyzed their experience of Gastric pull-up for cancers of the hypopharynx and cervical esophagus. Twenty-five cases of squamous cancer of the hypopharynx and cervical esophagus treated with laryngopharyngoesophagectomy and pharyngogastric anastomosis were presented. Twelve patients had received full radiation therapy and surgery was undertaken for residual and recurrent disease. Eleven patients had a concurrent unilateral radical neck dissection and two patients a concurrent bilateral neck dissection. Five patients died within 1 month following surgery. The most notable features of this method of pharyngeal and cervical esophageal reconstruction is the early restoration of swallowing (20 patients were on oral feed in less than 10 days following surgery), a very low incidence of anastomatic leak and subsequent hazards of a carotid hemorrhage (only one patient had a major leak leading to carotid hemorrhage), and absence of subsequent anastomotic stenosis as is seen after reconstruction with skin tubes.

ISELI[27] et al published their functional outcomes results following Total paryngolaryngectomy. They have analyzed 18 patient undergoing total laryngopharyngectomy between July 2001 and July 2006 were prospectively recorded in a head and neck database. Out of eighteen patients who underwent laryngopharyngectomies with 5 having failed chemoradiotherapy and 13 presented with locally advanced tumours. Patients were reconstructed using free jejunal interposition if the lower anastomosis was in the neck (50%). They developed early fistulas (33%), late strictures (33%) and 44% spoke

with a tracheo-oesophageal puncture, the rest with an electrolarynx. If the lower anastomosis was below the manubrium, patients required a gastric pull-up (38.9%). Gastric pull-up patients had fewer fistulas but more number of chest complications. More gastric pull-up patients tolerated solid diet and 43% managed oesophageal speech, the remainder using an electrolarynx. Overall, 88.9% of jejunums and 100% of gastric pull-ups tolerated oral alimentation and 100% used verbal communication. During a mean follow up of 34 months, 7 patients (38.9%) died; four patients died of local recurrence, two of distant metastases and one of unrelated causes. They concluded surgical treatment of neoplasms of the hypopharynx and cervical oesophagus is technically demanding and involves careful postoperative care to manage complications. Despite having a poor tumour-related prognosis, laryngopharyngectomy may be carried out in selected patients with low mortality and acceptable functional and survival results.

D. F. Harrison [28] et. al between the years 1965 to 1977, 58 patients with advanced hypopharyngeal squamous carcinoma were treated by pharyngolaryngoesophagectomy and total thyroidectomy. Operative mortality for potentially curable cases was 8.6%, with a crude three-year survival rate of 29% for all cases. Mortality was 37% for patients with postcricoid tumors. Long-term management was uncomplicated except for calcium metabolism; two patients died from nephrocalcinosis secondary to return of circulating parathyroid hormone.

Krespi YP[29] et. al. published their study on hypoparathyroidism following total laryngopharyngectomy and gastric pull-up .They were using the gastric pull-up technique for closure of large pharyngoesophageal defects after radical oncological surgery since

1979. The management of severe hypocalcemia and hypovitaminosis D they seemed more difficult in patients undergoing pull-up reconstruction than in patients undergoing the same extirpative surgery, but reconstructed with more traditional methods. To determine if hypocalcemia and hypovitaminosis D were more common in gastric pull-up patients, and if postoperative management of these conditions is more problematic in this group, they retrospectively compared three groups of head and neck surgery patients. Group 1 consisted of 17 patients undergoing total laryngectomy with thyroid complex preservation. Group 2 consisted of 7 patients undergoing mediastinal dissection with total laryngectomy-thyroidectomy previously or concurrently. Group 3 consisted of 30 patients undergoing total laryngopharyngoesophagectomy-thyroidectomy and gastric pull-up reconstruction. The incidences of hypocalcemia requiring therapy were 12%, 50%, and 73%, respectively, with an overall incidence of 51%. The average amounts of supplemental calcium and vitamin D in the three groups were compared. A significant between the three groups was noted. They conclude that any patient should be carefully monitored for the signs and symptoms of hypocalcemia after major head and neck surgery. In the special instance of the gastric pull-up patient, calcium requirements and the range of serum calcium fluctuation are greatly increased compared to patients undergoing more traditional methods of reconstruction.

Kelly A[30] et. al. published their review results on outcomes of long-term swallowing TLPO with gastric transposition reconstruction. Ten patients underwent clinical examination and completed the performance status scale for head and neck questionnaire and also a gastric pull-up swallowing questionnaire designed for this review. Nine of the 10 patients

underwent videofluoroscopic examination of swallowing. One patient had a stricture at the orogastric anastomosis, and one patient had bilateral tongue immobility secondary to XIIth nerve palsies. Eight participants reported eating a normal diet, and five reported not limiting their eating environment. Regurgitation, slower eating and reduced capacity were the most common functional limitations. They concluded that gastric pull-up procedure has good swallowing outcomes, and indicate that such outcomes continue in the long term.

Shenoy[31] et al analyzed the mortality and morbidity following TLPO with pharyngogastric anastamosis done as a single-stage procedure. The technique employed was esophageal extraction by stripping method followed by gastric pull up. In 104 patients transportation of the stomach was done through posterior mediastinum and in one patient through presternal route. Significant post-operative complications included pharyngocutaneous fistula in 15 patients (14.3%) and pneumonitis in 20 patients (19%), fifteen patients (14.3%) died due to the causes related to surgery. All patients who survived were able to swallow solid and liquid food, on an average of 14 days post-operatively. They concluded that the stomach as a conduit following TLPO is a procedure which has given satisfying results when done in carefully selected patients.

Al Ghamdi SA[32] et al published their study on Pharyngolaryngo-esophagectomy with immediate gastric pull-up. Fifteen patients with carcinoma of the hypopharynx and cervical esophagus underwent TLPO with immediate gastric pull-up procedures over a period of nine years at the Asir Central Hospital in the southwestern region of Saudi Arabia. The most common complication was cervical fistula, which with its sequelae occurred in 40%. Postoperative function in terms of swallowing ability was good but rehabilitation of speech

was poor. The overall hospital mortality was 7%, and the crude survival rate was 40%. The most common cause of long-term failure was the recurrence of the disease. They concluded that the success of this operative procedure depends on wide surgical excision of cancer along with rapid reconstruction of alimentary canal.

Schilling MK et al[33] analyzed results of long-term survival of patients with stage IV hypopharyngeal cancer: impact of fundus rotation gastroplasty. They have included patients admitted with circular hypopharyngeal cancer and extension to the esophagus were enrolled in a multidisciplinary treatment protocol, including circular laryngopharyngoesophagectomy with tracheostomy, neck dissection, and pull-up of a fundus rotation gastric tube that was anastomosed to the oropharynx. Five weeks postoperatively high-dose radiotherapy (60 Gy) was given to the cervical region. Altogether, 18 qualifying patients were explored cervically, were found to have resectable lesions (i.e., without carotid artery infiltration), and were included in the protocol. After laryngopharyngoesophagectomy, an elongated gastric tube was pulled up to the oropharynx. The average distance bridged with the tube was 32 +/- 4 cm. No anastomotic leaks were found on postoperative Gastrografin swallow, and oral feeding was started between days 5 and 8. Patients were discharged with normal oral feeding on day 21 (+/- 17 days). Diarrhea, postprandial fullness, and reflux resolved within 6 months postoperatively. Five patients died during the follow-up period of 42 months (range 3-63 months): three due to cardiac events 18 and 38 months postoperatively and two within 12 months with residual disease and tumor recurrence, respectively. The estimated 5-year survival was 60%. We concluded that an aggressive multidisciplinary approach including TLPO, neck dissection, and high-

dose radiotherapy ascertains good long-term survival and good functional results in patients with advanced hypopharyngeal cancer when the intestinal continuity is reconstructed with a fundus rotation gastroplasty.

Samir A[34] et al published results of mortality and morbidity of primary pharyngogastric anastomosis following circumferential excision for hypopharyngeal malignancies. Seventy-five patients underwent gastric transposition for replacement of the pharyngoesophagus. These patients had primary or recurrent malignant tumors of the hypopharynx, postcricoid region, and cervical esophagus. The operative procedure consisted of a transhiatal esophagectomy and gastric pull-up to establish gastrointestinal continuity, with a unilateral or bilateral neck dissection where indicated. Seven patients died a mortality rate of 9.33%. The average hospital stay of uncomplicated cases was 18 days and for complicated cases was 40 days. Immediate restoration of oral intake was achieved in 70.6% of patients. They conclude that gastric transposition after circumferential laryngopharyngeal excision is a procedure with low mortality and acceptable morbidity leading to early relief of dysphagia.

S. B. Dudhat[35] et al analyzed Complications following gastric transposition after total laryngo-pharyngectomy. **A** retrospective analysis of 60 patients undergoing total laryngo-pharyngectomy with gastric transposition was performed between June 1991 and June 1996. The analysis focused on morbidity, mortality and long-term function following gastric transposition. The post-operative mortality was 8.3% and the peri-operative morbidity 31.2%. The average hospital stay was 15 days. Immediate restoration of swallowing was achieved in 83% of patients. They concluded gastric transposition after total laryngo-pharyngectomy is a safe procedure and can be performed with low mortality,

acceptable morbidity and good long-term function.

Z. Ferahkose[36] et al published their results on comparison of free jejunal graft with gastric pull-up reconstruction after resection of hypopharyngeal and cervical esophageal carcinoma. They evaluated the operative outcomes of a gastric pull-up and free jejunal graft reconstruction after resection of hypopharyngeal and cervical esophageal carcinoma. Records of all patients who underwent esophageal resection for carcinoma of the hypopharynx and cervical esophagus were reviewed. Reconstruction after esophagectomy was performed using the gastric pull-up ($n = 38$) or free jejunal graft ($n = 14$) techniques. The hypopharynx was the most common primary tumor site for the free jejunal graft group, whereas the gastric pull-up group had lesions more frequently in the cervical esophagus ($P < 0.05$). Both operative time and blood loss in the gastric pull-up group were significantly longer and excessive than those of the free jejunal graft group ($P < 0.05$). The graft survival rate was 95% (32/34) in the gastric pull-up group and 93% (13/14) for the free jejunal transfer group. The overall leakage rate was 1.9% (1/52). Three patients died (6%) in the postoperative period. There was no significant difference with regard to operative morbidity and mortality between the gastric pull-up group and free jejunal graft group. They concluded, both free jejunal graft and gastric pull-up are safe and effective methods for the immediate restoration of alimentary continuity.

Jean-Pierre Triboulet[56] et al published results of Surgical Management of Carcinoma of the Hypopharynx and Cervical Esophagus a analysis of 209 Cases. They reviewed the records of patients who underwent total pharyngolaryngectomy between May 1982 and July 1999. The majority of patients had advanced cancer: hypopharyngeal in

131 cases and cervical esophageal in 78 cases. The postoperative in-hospital mortality rate was 4.8% (10 patients), with a postoperative morbidity rate of 38.3%. Alimentary continuity was achieved using the stomach (127 patients), colon (5 patients), or free jejunal autograft (77 patients). The 1-year and 5-year survival rates were 62% and 24%, respectively. There was no significant difference with regard to the survival between gastric transposition and free jejunal autograft, but there were fewer complications in the gastric pull-up group (33% Vs 47%, *P*_.05). The significant adverse factors affecting survival were tumor cervical localization, postoperative complications, disease stages pT3 and pT4 for the cervical esophageal tumors, microscopic pharyngeal penetration, or incomplete resection. The significant beneficial factors were tumor hypopharyngeal localization and postoperative radiotherapy. They concluded that surgical ablation is a viable option for advanced hypopharyngeal and cervical esophageal neoplasm, with stomach interposition the preferred method of reconstruction. Although the prognosis is poor, satisfactory short-term palliation can be achieved. The significant adverse factors affecting survival should be taken into account to select the candidates for surgery.

AIMS AND OBJECTIVES

The aims of this study are to analyze following outcomes of patient with advanced hypopharyngeal cancers treated with Total Laryngopharyngoesophagectomy (TLPO) with gastric tube reconstruction.

1. Surgical outcomes
2. Overall survival
3. Prognostic factors influencing survival
4. Recurrence patterns.

MATERIALS AND METHODOLOGY

The study was conducted in Cancer Institute (WIA), Chennai. Case records of 122 patients out of 608 patients with histologically confirmed hypopharyngeal cancer were reviewed who underwent TLPO over 6 years period from 2001 to 2006. There were 69 males and 53 females. TLPO was carried out in 120 patients and total laryngopharyngectomy was done in two patients. 101 patients underwent neck dissection along with TLPO and gastric pull up was done in 120 patients and free jejunal flap reconstruction was done in one patients. One patient underwent total laryngopharyngectomy and control pharyngostoma and 97 patients received adjuvant radiotherapy.

All the patient's were ECOG performance status 1. Patients underwent through clinical examination including indirect laryngoscopy, direct laryngoscopy and biopsy, and UGI endoscopy if possible, complete haematological examination, X-ray chest, Imaging of neck, chest and abdomen as required and histopathological confirmation of malignancy. All patients underwent detailed pre-anaesthetic check-up including cardiac and respiratory evaluation and optimization for surgery. Patients diagnosed to have carcinoma hypopharynx with clinical Stage III and IVA was included for surgery and tumor with circumferential involvement of hypopharynx, involvement of postcricoid growth or pyriform sinus growth with involvement of apex of pyriform sinus or extension into cervical esophagus were taken up for surgery.

SURGICAL DETAILS

All the patients were admitted before surgery and necessary supportive treatment was given before surgery.

SURGICAL TECHNIQUES

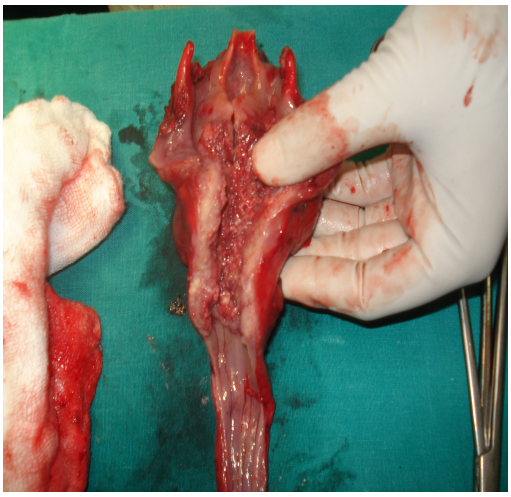
After endotracheal intubation adequate skin preparation was done from the face up to the upper thigh and draping was done as required. Skin flaps were raised subplatysmally through an apron incision and assessment of tumor resectability and extension was made. Neck dissection was done as necessary. Patient with N0 at presentation neck underwent bilateral level II to IV nodal dissection and patient with N+ under went either MRND or RND and level II to IV nodal clearance in N0 side. Circumferential mobilisation of the hypopharynx was done. Contralateral thyroid lobe was preserved after assessing the tumor extension. Pharynx was entered through the vallecula or through the contralateral pharynx and circumferentially divided with adequate gross clear margin. Trachea was divided with adequate margin.

Abdomen was opened through a midline upper abdomen incision and esophagus divide at esophagogastric junction after excluding any pathology in the stomach. Gastric tube was made based on right gastroepiploic vessels with linear cutting GI staplers. Vein stripper was introduced through the hypopharynx to esophagus down to abdomen and tied all-around at the lower end, stomach tube also connected with a long cotton tape and than stripper gently pulled with minimum force from the neck and esophagus stripped up-to the neck and specimen retrieved. Mediastinum is inspected for bleeding. Stomach tube is pulled up gently through posterior mediastinum without any twist and pharyngogastric end to end anastomosis was done in single layer, interrupted, either with 3-0 silk or 3-0 vicryl. Levator

scapulae muscle flap was used to cover carotid vessels in patient who under went RND or MRND. Complete haemostasis was achieved. Chyle leak was checked by applying positive pressure ventilation. Wound closed over two suction drains and tracheostoma matured. Feeding jejunostomy was done for all patients. All patients received broad spectrum antibiotics once at the time of induction of anaesthesia and continued upto 3rd postoperative day. Jejunostomy feeding was started on 1st postoperative day and increased gradually. Trial oral feeding was started on 8th postoperative day and was increased gradually based on patient tolerance. Radiotherapy was started within four to six weeks of surgery for most of the patient. Follow-up was done with history and clinical examination in each visit, X-ray chest yearly, Endoscopy as necessary. Frequency of follow-up was every monthly for first year, every alternate monthly in 2nd year and 3 monthly in 3rd year and 6 monthly for next two years and there after every yearly.

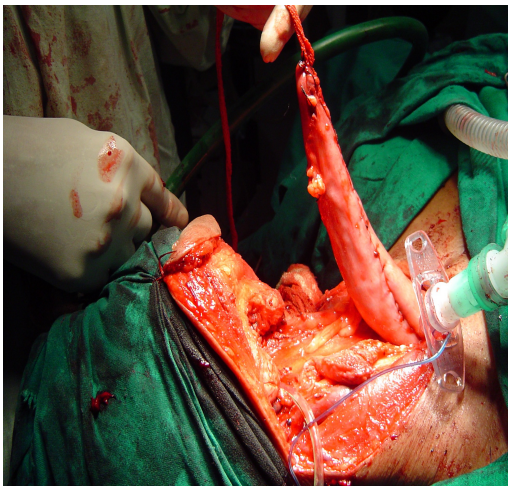
STATISTICAL ANALYSIS

Done by actuarial methods calculated using SPPS software.



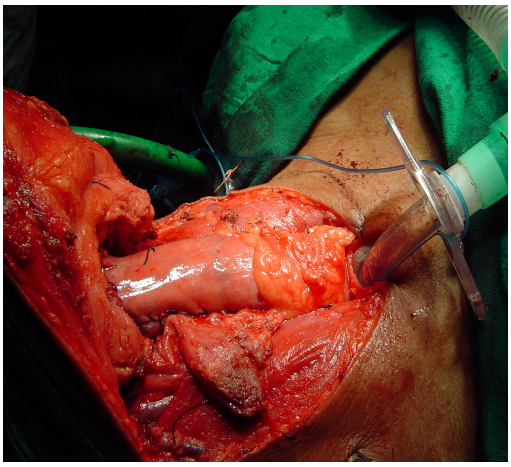
Pictures showing Laryngo Pharyngectomy Esophagectomy Specimen

Stomach tube ready for pull-up



Stomach tube in neck

After Pharyngogastric anastomosis

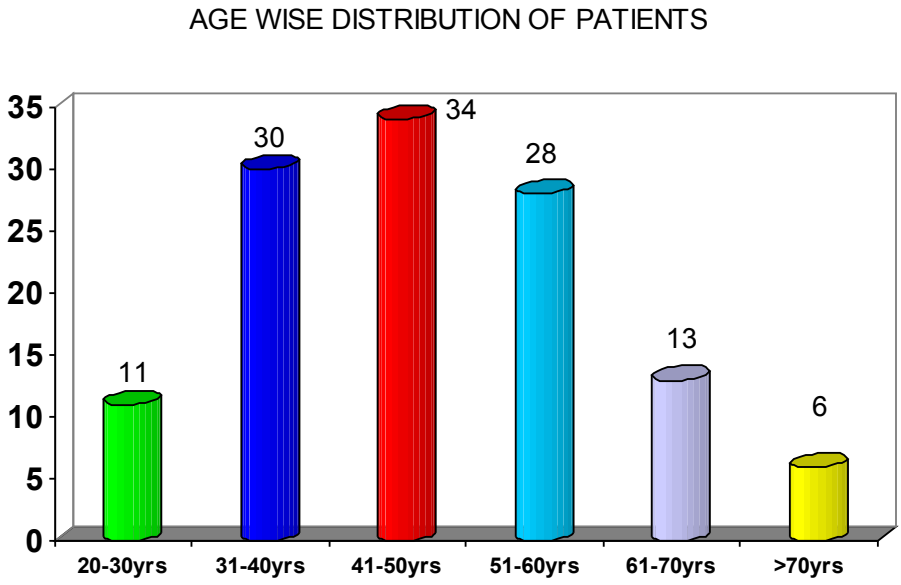


OBSERVATION AND RESULTS

Case records of 122 patients were analysed. Follow-up compliance was also ascertained. Patient who has not come for regular follow-up health condition were enquired by writing letter to their address or by telephone call. Four patients were lost to follow-up immediately after completion of treatment and details of their health condition could not be collected.

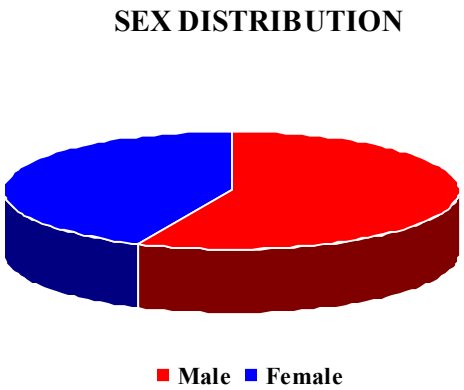
Follow-up periods for remaining patient ranging from 22 months to 72 months and median follow-up is 19.5months.

1. Age Distribution



In our series youngest patient was 23 years old and eldest patient was 76 years old. Most of the patients were 30 to 60 years of age. Median age is 47 years. Here we analyzed the specific subsets of hypopharyngeal cancer who underwent TLPO.

2.



Majority of patients are male. Though it is common in males but recently incidence of hypopharyngeal cancer is increasing in females.

2. Surgical procedures performed:-

Surgical excision		No of patients
Total laryngopharyngoesophagectomy (TLPO)	–	120
Total Laryngopharyngectomy	-	2
Neck dissection	-	101
Reconstruction**		
Gastric Pull – up	-	120
Free jejunal flap reconstruction	-	1
Controlled pharyngostoma	-	1

** One patient developed intraoperative hypotension after laparotomy and which was not improved after adequate support and hence only Total Laryngopharyngectomy and control pharyngostoma and feeding jejunostomy was done and gastric pull up was planned after stabilisation. But patient developed multiple medical complications postoperatively and expired due to septicaemia and multiorgan failure.

During initial 21 cases, clinical N0 at presentation neck dissection was not considered but subsequently all the patient under went neck dissection as required. Subsequent 61 patients with N0 at presentation underwent bilateral level II to IV nodal clearance and 40 patients N+ at presentation underwent MRND in N1 patients and in N2 patient underwent RND or extended RND. In few cases levator scapulae flap was used to cover carotid in the neck to prevent carotid blow out if there is salivary leak.

3. Histopathology Squamous cell carcinoma – 116

Poorly differentiated carcinoma – 4

Adenoid cystic carcinoma – 2

Table showing Pathological Stage distribution:

Variables	No of pts	Total
Stage PII PIII PIVA	 7 38 77	 122
T Status PT2 PT3 PT4a	 12 57 53	 122
N Status PN0 PN1 PN2 Nx (ND not done)	 41 17 43 21	 122

116 patients were of Squamous cell carcinoma and 60 patients were node positive out of 101 neck dissection patients. 77(63%) patients were of pathological stage IVA, 38 patients of Stage III and 7 patients of Stage II. Pathological T3 & T4a consists of 110 (90%) patients.

5. ADJUVANT RADIATION THERAPY (RT)

97 patient out of 122 received adjuvant radiotherapy. 7 patients were clinically though advanced stage disease but on pathological staging was of early stage disease and hence adjuvant RT was not considered, and few patients because of complications radiotherapy

could not be started on time and hence post operative RT not received. Most of the patient received 50 to 60 Gy RT.

Total dose of RT (Gy)	No of patient's
< 50	21
50-60	75
>60	1
Total	97

6. HOSPITAL SHORT TERM - MORBIDITY AND MORTALITY

POSTOPERATIVE MORTALITY

5 (4.06%) patients expired within 30 days of surgery. One patient died of DIC on 8th postoperative day. Three patients expired because of sudden cardiac arrest within 30days of surgery and one patient expired on 27th postoperative day because of septicaemia and multiorgan failure. Out of this 5 patient one patient had stomach tube necrosis.

MORBIDITY

Significant postoperative complications occurred in 40 patients (32.78%). Twenty-seven anastomotic leaks (22%) were observed, out of which 10 patient required surgical interventions for fistula closure. 17 patients had minor leak which were completely resolved on regular dressing. There were 6 stomach tube necrosis. This were salvaged by free jejunal flap reconstruction in 2, colonic pullup in one patient, Pectoralis Major myocutaneous flap (PMMC) reconstruction in 4 patients, by the use of a deltopectoral myocutaneous flap in 1 patient.

Table showing various complications

Variables	No of patients	%

Salivary leaks	27	22.13
Major	10	8.19
Minor	17	13.9
Hypocalcemia	10	8.1
Stomach tube necrosis	6	4.9
Chyle leak	2	1.63
Carotid blow out	1	0.8
Wound complications	6	4.9
Pharyngotracheal fistula	1	0.8
Septicaemia	3	2.45
Intestinal Obstruction	1	0.8
Pulmonary complication	3	2.45

Two patients underwent thoracotomy and ligation of thoracic duct. Three patients were on ventilator support for long time for pulmonary complications. Patient who developed pharyngocutaneous fistula healed spontaneously following conservative management within 2weeks.

Morbidity in neck dissection patients

Neck dissection		Complications				
		Present			Absent	
	No of pts	No of pts	%	P value	No of pts	%
Done	101	32	31.68	NS	69	68.31
Not Done	21	8	38.09		13	61.9

Salivary leak according to neck dissection

Neck dissection		Salivary Leak			
		Present		absent	
		No of pts	%	No of pts	%
	Total				
Not done	21	7	33.33	14	66.66
Done	101	20	19.8	81	80.19

Salivary leak occurred in 7(33.33%) patients out of 21 patients where neck dissection was not considered and 20 (19.8%) patients out of 101 patients who underwent neck dissection. It appears from here that neck dissection does not associated with increased in morbidity.

Trial oral feeding was started on 8th postoperative day and depending on tolerance gradually increased. Few patient oral feeding was started on 4th postoperative day and patient could tolerate. The average time of resumption of oral feeding was 12days and 66% of patient resumed oral feeding within 15 days of surgery.

Once patient could tolerate normal diet they were discharged and were called for adjuvant radiotherapy with 1 to 2 weeks gap. The average hospital stay for the whole population was 18 days (range 8-45days).

7. OVERALL SURVIVAL AND ONCOLOGICAL RESULTS

Tumor recurrences occurred in 41 patients (33.6%). Median time to recurrence 8months (Range 1-27months). Local recurrence as first failure occurred in 14 patients, only regional recurrence occurred in 12 patients and distant recurrence

occurred in 9(7.3%) patients. Most of these recurrence cases presented in advanced disease or poor performance status and hence most of them received on symptomatic treatment.

Disease free survival and overall survival at 3 years was 39% and 43% respectively. The 5 year over all survival was 34%.

To identify prognostic factors, we evaluated the survival rates for each of the following parameters, as presented in following table. Only four of the possible prognostic factors were found to actually influence survival: Pathological Stage, Pathological T status and postoperative complications, post operative radiotherapy (P=0.008) in univariate analysis. In the subset of

of patients with bilateral selective lateral neck dissection PN0 versus PN2 5 year over all survival (51.4% Vs 21.6%) stastically significant(*P*-0.03). In multivariate analysis only pathological Stage was found to be prognostic factor for survival.

Overall Survival: Prognostic Parameters Issued From the Univariate Analysis

Variables	No of pts	Recurrence		5 year over all survival	
Stage			%		P value
PII	7	1	14.2	64.29	.0505
PIII	38	9	23.7	50.98	
PIVA	77	32	41.6	23.36	2Vs4 0.04
T Status					.0996
PT2	12	3	25	45.88	
PT3	57	17	29.8	44.37	3Vs4
PT4a	53	22	41.5	22.03	.046
N Status					
PN0	41	10	24.4	53.0	NS
PN1	17	5	28.5	46.7	
PN2	43	16	29.4	37.8	

Nx (ND not done)	21	11	52.4	20.5	
Post OP RT Yes No	 97 25	 38 42	 39.2 16	 35 31	.0081
Morbidity Yes No	 40 82	 18 23	 45 28	 26 39	.0060
Sex Male Female	 69 53	 29 13	 42 24.5	 25 48	.57

Table showing Survival pattern according to neck dissection

Neck dissection	No of pts	Recurrence		Regional recurrence		5 years OS %	P value
		No of pts	%	No of pts	%		
A*	21	11	52.38	6	28.57	33.3	0.50
B*	61	17	27.86	5	8.19	37.7	
C*	40	13	32.5	6	15	33.3	

* A – Neck dissection not done, B – Bilateral lateral selective neck dissection, C – Therapeutic neck dissection

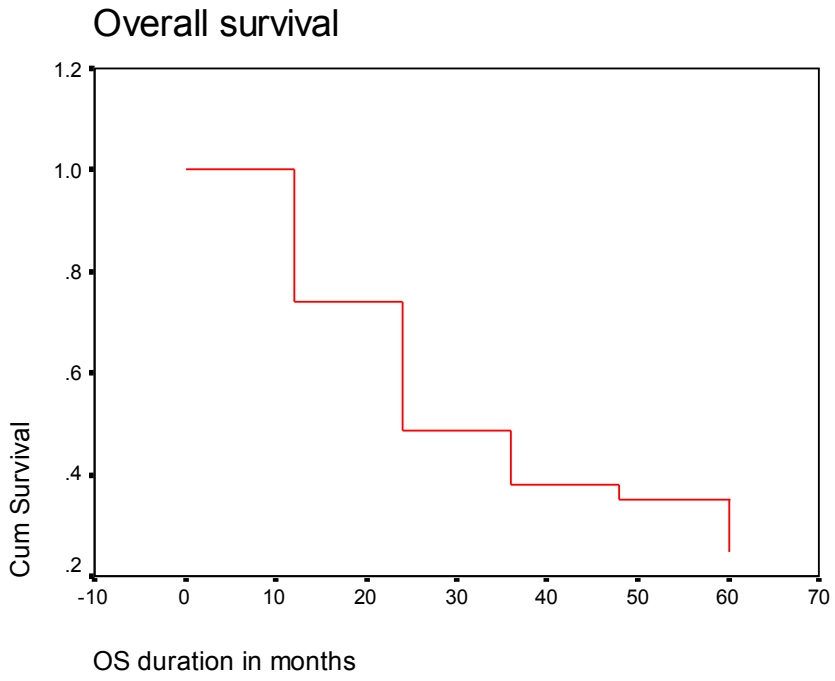
Table showing results of bilateral lateral selective neck dissection.

Path N status	No of Patients	%	Recurrence		Regional recurrence		5 year OS %	P value
			No	%	No	%		

PN0	28	45.9	7	25	2	7.14	51.4	0.10 NS
PN1	11	18	3	27.27	1	9.09	33.06 at 4 years	PN0 Vs PN2 = .03
PN2	22	36.1	7	31.81	2	9.09	21.6	
Total	61		17	27.86	5	8.19		

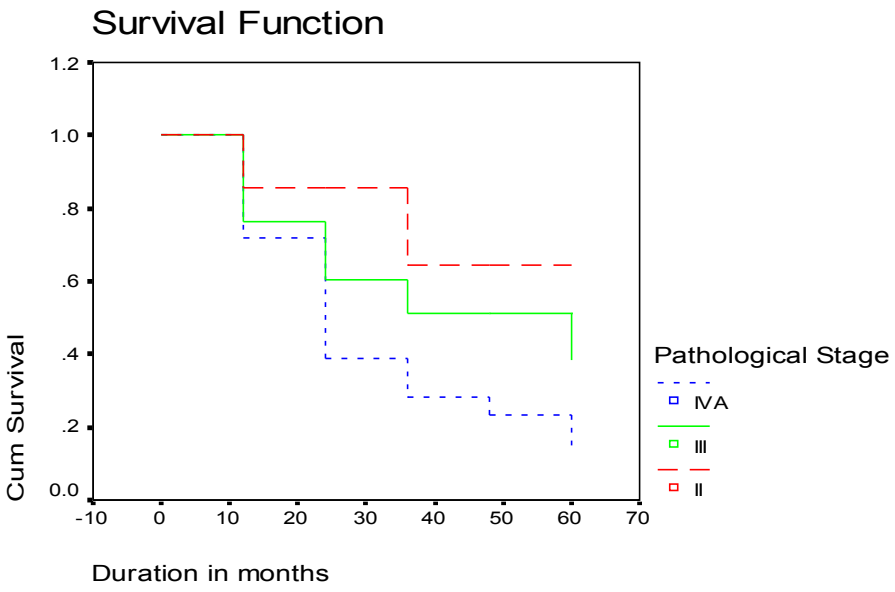
Total 61 patients N0 at presentation underwent bilateral level II to IV nodal dissection and out of which 33(27%) patients found to have occult nodal metastasis which is similar to various study[11]. Out of 61 patient 17 patients developed recurrence, and among these 5 (8.19) patients in develop nodal recurrence, 2(7.14%) patients in PN0, 1(9.09%) patient in PN1 and 2(9.09%) patients in PN2 recurred in neck. Survival PN0 versus PN2 is stastically significant (P- 0.03). In PN1 group non of the patient completed 5 years follow-up till the study period and hence 4 years overall survival is considered.

1. OVERALL SURVIVAL CURVE

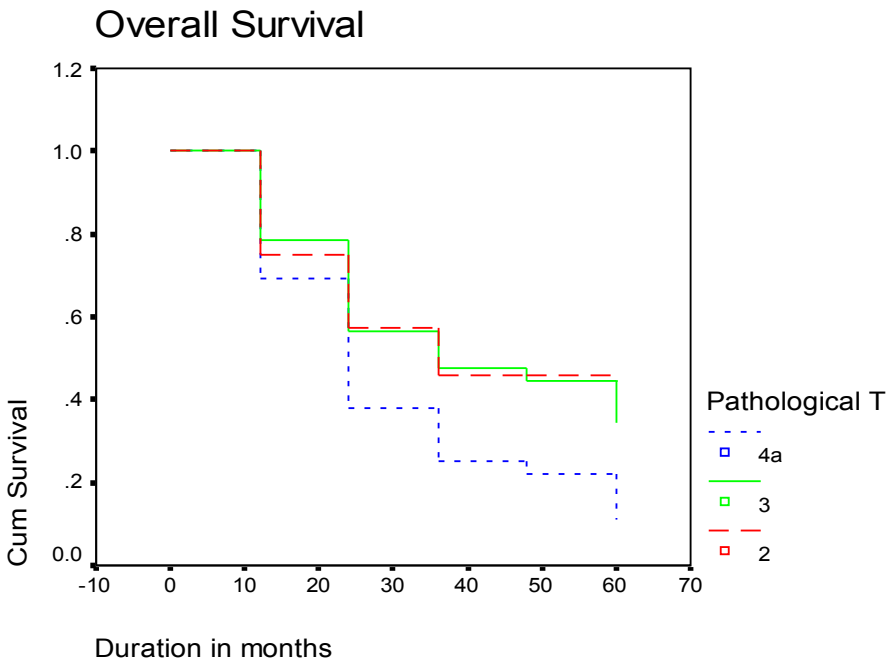


5 year over all survival 34%

2. SURVIVAL ACCORDING TO PATHOLOGICAL STAGE

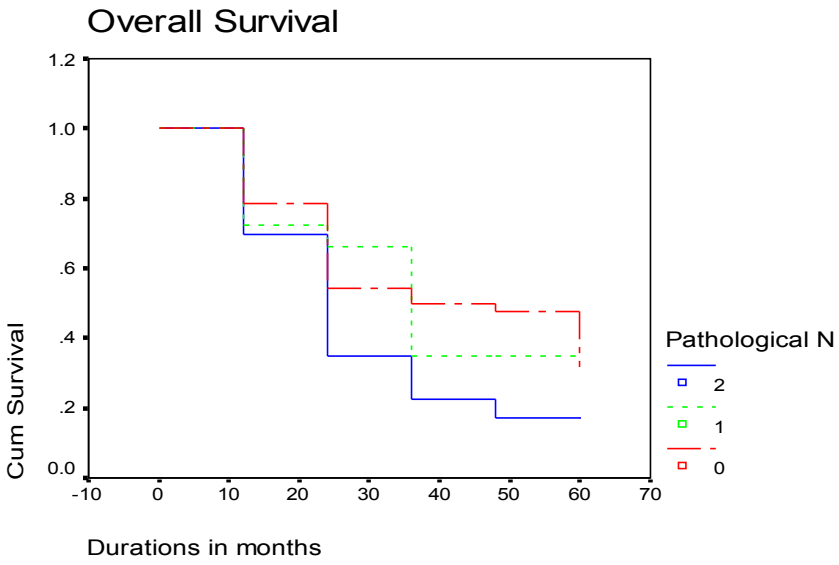


3. SURVIVAL ACCORDING TO PATHOLOGICAL T STATUS



Overall survival difference was not significant according to pathological T status, but there was definite statistical significance of survival difference between PT3 Vs PT4a

3. SURVIVAL ACCORDING TO PATHOLOGICAL N TATUS



DISCUSSION

Management of carcinoma of the hypopharynx is a challenge to the head and neck surgeon ([50, 51]. Various techniques have been utilized to effect pharyngeal continuity with each with varying morbidity and mortality [52]. The optimal reconstructive procedure should provide the lowest mortality and morbidity, the shortest hospital stay, and the most rapid return to successful feeding [53, 54]. At present, no general criteria exists as to which methods is the perfect reconstruction method after TLPO. Over the last 40 years, the use of stomach as a method of reconstruction has become one of the most popular method of reconstruction [49].

MORTALITY:

Several series have reported mortality rates ranging from 5% to 55% [2, 45, 38, 47,]. In the study by Shenoy RK[31] et al 30 days postoperative mortality was 14.3% and in S. B. Dudhat[35] et al series postoperative mortality was 8.3% and in the study by Jean-Pierre Triboulet[56] 30 days postoperative mortality rate was 4.8% and in our study 30 days postoperative mortality was 4.06% which is similar.

MORBIDITY:

In choosing the reconstructive method, post operative complications are very important factor. Several series have reported acceptable morbidity ranging from 5 to 31%[2,45,38, 47,] . In the present study morbidity was 32.78 which is comparable to other studies.

SALIVARY LEAK:

Among the complications majority was salivary leak ranging form 7% to 37% leakage rates reported in various study [2, 45-47]. The incidence of clinically evident anastomotic

leakage has decreased in the last 5 years to 10.5% for Bardini[55] et al and to 4.5% as quoted by Lam et al[45]. In the study by Shenoy RK[31] et al following TLPO 15 (14.3%) patients out of 104 patients developed anastomotic leak. In the study by Jean-Pierre Triboulet[56] et al forty-seven out of 209 patients had anastomotic leaks (22.5%), including 11 patients that were clinically evident and 36 patients were asymptomatic but detected radiologically, and that closed without surgical correction. Where free jejunal grafts had been used, the fistulas always occurred proximally. In the present study 27 (22%) patients out 122 patients developed anastomotic leak and among which 10 (8%) required surgical intervention which is similar to above study. Stomach tube was necrosed in 5 patients out of 127 gastric tube transpositions in the above mentioned study by Triboulet[56] et al and in our study 6 patients had stomach tube necrosis out of 122 patients which is similar.

PULMONARY COMPLICATION:

Pulmonary complication following TLPO reaches upto 20% in various studies [57.58], In the study by Shenoy RK[31] et al 20(19%) patients developed pneumonitis following TLPO. In our study only 3 (2.45%) patients had severe pulmonary complication which required ventilator support for a long time postoperatively and improved subsequently. In the study by Jean-Pierre Triboulet[56] four patient died because of pulmonary infections. But in our study there was no death because of pulmonary complication.

HYPOCALCEMIA:

Another common complication following TPLO is hypocalcemia. In the study by Krespi YP[29] et al following TLPO 73% of their patients developed hypocalcaemia. Management of

these patients required a combination of oral and intravenous calcium supplement and many patient required vitamin D supplementation as well. In our study 10 (8%) patients developed severe hypocalcemia and which required intravenous calcium injection in immediate postoperative period and subsequently improved on oral calcium and Vitamin D supplement.

INFECTIOUS COMPLICATIONS:

Wound infection developed in 6 (4.9%) of our patients which is lower than previous reported study by **J. Rezaie1** [58] which is 10%.

Carotid blow out one of the rare life threatening emergency complication which may occur following laryngopharyngeal resection if associated with neck dissection. One of our patients who had salivary leak developed carotid artery blow out on 7th postoperative day for which emergency carotid artery was ligated to save the patient and following that there was no neurological deficit and subsequently patient underwent jejunal free flap reconstruction for fistula closure.

Chyle leak one of the complication following neck dissection most of the time in the left side and most of the times leak stops on conservative management. Two of our patients developed chylothorax and persisted despite of intercostals drainage(ICD) and hence underwent thoracotomy and ligation of the thoracic duct on 8th and 14th postoperative day.

RESUMPTION OF ORAL FEEDING

The major goal of the TLPO is early resumption of the oral feeding. Most of the patients present with varying forms of dysphagia. In the study by Jean-Pierre Triboulet[56] et al the average time of resumption of feeding was 19.7 days following the operation

(range, 0-700 days). Excluding the postoperative deaths, swallowing was achieved in 98.4% of patients. Only 3 patients were not able to swallow after recovering from the procedure: 2 because of necrosis of the jejunal graft and 1 because of a major swallowing disorder. In our study 66% of patient resumed oral feeding within 15 (range 4-90days) days of surgery and excluding the postoperative deaths swallowing was achieved in all patients.

AVERAGE HOSPITAL STAY

In the study by Jean-Pierre Triboulet[56] et al the average hospital stay for the whole population was 23.6 days (range, 1-240 days). In our study average hospital stay was 18 days (range 8-45days) which is similar.

RECURRENCE

In the study by Jean-Pierre Triboulet[56] tumor recurrences occurred in 118 patients (59.3%), with a mean delay of 19 months (range, 1-104 months).

These patients were treated by chemotherapy, radiotherapy, or neck dissection. Local recurrence alone occurred in 46 patients and was combined with neck recurrence in 48 patients. Distant metastases were found in 22 patients, and 2 patients had tumor recurrences at unknown sites. In our study 41 (33.6%) patients developed recurrence and median time to recurrence was 8 months (range 1-27 months). Most of the patients presented with advanced disease or with poor performance status and hence most of them were treated with symptomatic

treatment only. Local recurrence as first failure occurred in 14 patients, only regional recurrence occurred in 12 patients and distant recurrence occurred in 9(7.3%) patients.

OVERALL SURVIVAL:

The overall 5-year survival rates for advanced Squamous cell carcinomas of the hypopharynx has not changed significantly, despite advances in surgical techniques, chemotherapy, and radiation therapy. Actuarial 5-year survival rates reported in the literature range from 18% to 35% regardless of therapy [2, 38-44]. In the study by Jean-Pierre Triboulet[56] 5 year overall survival was 29%. and in our series, the overall 5-year survival rate was 34% which is similar the various study.

CONCLUSION

Surgical resection followed by adjuvant radiotherapy remains the standard of treatment for advanced hypopharyngeal carcinoma and gastric interposition is the preferred method of reconstruction for circumferential defect. In our study the mortality and morbidity rates were comparable with other studies. Prophylactic bilateral level II to IV nodal clearance should be considered for patients with N0 at presentation as there were no increase in morbidity by doing neck dissection and there was high percentage of occult nodal metastases in our study and specifically, the difference in long term survival is statistically significant among PN0 versus PN2 (P=0.03) in this subset of patient, where we can consider modification in

adjuvant therapy. Overall survival in our study is comparable with other studies. In our study prognostic factors which influenced overall survival were: Pathological Stage (Stage II Vs Stage IVA, P=0.04), pathological T status (PT3 versus PT4, P=0.046), postoperative complications (P=0.0060) and adjuvant radiotherapy (P=0.008). Organ preservation strategies have not been as successful in hypopharyngeal cancers as for cancers of other head and neck sites. Further studies will be necessary to compare the use of chemoradiotherapy, larynx preservation, and surgery in terms of overall survival and quality of life, especially the ability to continue oral feeding.

REFERENCES

1. Hoffman HT, Karnell LH, Funk GF, Robinson RA, Menck HR. The National Cancer Data Base Report on cancer of the head and neck. Arch Otolaryngol Head Neak Surger 1998;124:951-62.

2. Carlson GW, Schusterman MA, Guillamondegui OM. Total reconstruction of the hypopharynx and cervical esophagus: a 20-year experience. *Ann Plast Surg.* 1992; 29:408-412.

3. Ho CM , Lam KH, Wei WI, Yuen PW, Lam LK. Squamous cell of the hypopharynx - analysis of treatment results. Head and Neck 1993; 15: 405-12.

4. Shah JP, Shah AR, Spiro RH, Strong EW, Carcinoma of the hypopharynx. Am J Surg 1976; 132: 439 -43.

5. Lefebvre JL, Castelin B, DeLa Torre JC Delobelle-Deroide A, Vankemmel B, Lymph node invasion in hypopharynx and lateral epilarynx: a prognostic factor. Head Neck Surg 1987; 10:14-8

6. Johnoson JT, Bacon GW, Myers EN, Wagner RL, Medial vs lateral wall pyiform sinus carcinoma: implications for management of regional lymphatics. Head Neck 1994; 16:401-5.

7. Karus DH, Zelefsky MJ, Brock HA, Huo J, Harrison LB, Shah JP, Combine surgery and radiation therapy for squamous cell carcinoma of hypopharynx. Otolaryngol Head Neak Surgery 1997; 116:637-41.

8. El Badawi SA, Goepfert H, Fletcher GH, Herson J, Oswald MJ, Squamous cell carcinoma of Pyriform sinus. Laryngoscope 1982;92:357-64.

9. Candela FC, Kothari K, Shah JP, Patterns of cervical node metastases from squamous cell carcinoma of oropharynx & hypopharynx. Head Neck 1990;12:197-203.

10. Mukherji SK, Armao D, Joshi VM. Cervical node metastases in squamous cell carcinoma of the head and neck : what to expect. Head Neck 2001:23:995-1005.

11. Buckley JG, MacLennan K. Cervical nodal metastases in laryngeal and hypopharyngal cancer: a prospective analysis of prevalence and distribution. Head Neck 2000: 22: 380-5.

12. Amatsu M, Mohri M, Kinishi M. Significance of retropharyngeal node dissection at radical surgery for carcinoma of the hypopharynx and cervical esophagus. Laryngoscope 2001; 111: 1099-103.

13. Frank JL, Garb JL, Kay S, Mc Clish DK, Bethke KP, Lind DS, et al. Postoperative radiation therapy improves survival in squamous cell carcinoma of the hypopharynx. Am J surg 1994;168:476-80.

14. James A. Bonner, M.D., Paul M. Harari, M.D., Jordi Giralt, .D.,Radiotherapy plus Cetuximab for Squamous- Cell Carcinoma of the Head and Neck. *N Engl J Med* 2006;354:567-78.

15. Wei WI. The dilemma of treating hypopharyngeal carcinoma: more or less. Arch Otolaryngol Head Neck Surg 2002; 128:229-32.

16. Carl E Silver and Roger J. Levin, Surgery for Cancer of the Larynx and Related Stuctures, 2nd edition. Chapter 9.254-257.

17. Denk W. Zur Radikaloperation des Oesophaguskarizinomas. *Zentralbl Chir* 1913; 40:1065-1068.

18. Turner GG. Carcinoma of the esophagus: the question of its treatment by surgery. Lancet

1936;1:67-74

19. Turner GG. Carcinoma of the esophagus: the question of its treatment by surgery. Lancet 1936;1:130-134.

20. Ong GB, Lee TC. Phryngogastric anastomosis after oesophagopharyngectomy for carcinoma of the hypopharynx and cervical esophagus. *Br J Surgery* 1960; 48: 193-200.

21. Le Quesne LP, Ranger D. Pharyngolaryngectomy with immediate pharyngogastric anastomosis. *Br J Surg* 1966;53: 105-109.

22. Stell PM. Esophageal replacement by transposed stomach. *Arch Otolryngol* 1970; 91: 166-170.

23. Leonard JR, Maran AG. Reconstruction of the cervical esophagus via gastric anastomosis. *Laryngoscope* 1970; 80: 849-862.

24. Silver CE. Gastric pull-up operation for replacement of the cervical portion of the esophagus. *Surg Gynecol Obstet*. 1976; 142: 243-245.

25. Parkin DM, Muir CS, Whelan SL, et al: Cancer Incidence in Five Continents, vol VI. Lyon, IARC Scientific publications, 1992.

26. ***Pradhan SA***, ***Rajpal RM***. *Gastric pull-up for cancers of the hypopharynx and cervical esophagus: our experience.* ***J Surg Oncol. 1984 Jun;26(2):149-52.***

27. ISELI, TIM A. FRACS, PGDipSurgAnat; AGAR, NICHOLAS J. M. MB BS; DUNEMANN, CATHERINE BSPath +; LYONS, BERNARD M. FRACS Functional outcomes following Total Pharyngolaryngectomy, ANZ Journal of Surgery. 77(11):954-957, November 2007.

28. D. F. Harrison Surgical management of hypopharyngeal cancer. Particular reference to

the gastric "pull-up" operation ARCHIVES OF OTOLARYNGOLOGY – HEAD & NECK SURGERY Vol. 105 No. 3, March 1979

29. Krespi YP, Wurster CF, Wang TD, Stone DM Hypoparathyroidism following total laryngopharyngectomy and gastric pull-up, Laryngoscope. 1985 Oct;95(10):1184-7

30. ***Kelly A****,* ***Drinnan MJ****,* ***Savy L****,* ***Howard DJ*** *Total laryngopharyngoesophagectomy with gastric transposition reconstruction: review of long-term swallowing outcomes.* **.** ***J Laryngol Otol. 2008 May 19:1-6***

31. Shenoy RK, Pai SU, Rajan N Department of Surgery, Kasturba Medical College, Manipal. Stomach as a conduit for esophagus--a study of 105 cases Indian J Gastroenterol. 1996 Oct;15(4):52-4

32. Al Ghamdi SA et al published their study on Pharyngolaryngo-esophagectomy with immediate gastric pull-up, Department of Otolaryngology, College of Medicine, King Saud University, Abha, Saudi Arabia. Ann Saudi Med. 1998 Mar-Apr;18(2):132-4.

33. Schilling MK, Eichenberger M, Maurer CA, Greiner R, Zbären P, Büchler MW Long-term survival of patients with stage IV hypopharyngeal cancer: impact of fundus rotation gastroplasty, World J Surg. 2002 May;26(5):561-5. Epub 2002 Feb 25

34. Samir A. Mehta, MS [1], Sudeep Sarkar, MS [1], Dr. Ashok R. Mehta, MS, FICS [1 *], Mona S. Mehta, [1]Head & Neck Service "C," Department of Surgical Oncology, Tata Memorial Hospital, Bombay, India [2]Department of Radiology, Tata Memorial Hospital, Bombay, India Mortality and morbidity of primary pharyngogastric anastomosis following circumferential excision for

hypopharyngeal malignancies, Seminars in Surgical Oncology Volume 43 Issue 1, Pages 24 – 27, 20 Jul 2006

35. S. B. Dudhat, R. C. Mistry and A. R. Fakih Tata Memorial Hospital, Parel, Mumbai 400 012, India. Complications following gastric transposition after total laryngo-pharyngectomy, European Journal of Surgical Oncology Volume 25, Issue 1, February 1999, Pages 82-85

36. **Z. Ferahkose, [1] A. Bedirli, [1] M. Kerem, [1] C. Azili, [1] E. M. Sozuer, [2] M. Akin Gazi University Medical Faculty, Department of General Surgery, Ankara, Turkey and [2] Erciyes University Medical Faculty, Department of General Surgery, Kayseri, Turkey** Comparison of free jejunal graft with gastric pull-up reconstruction after resection of hypopharyngeal and cervical esophageal carcinoma, **Diseases of the Esophagus Volume 21 Issue 4, Pages 340 – 345 Published Online:** 14 Sep 2007

37. Hoffman HT, Karnell LH, Shah JP, Ariyan S, Brown GS, Fee WE, et al. Hpopharyngeal patient care evaluation,. Laryngoscope 1997: 107: 1005-17.

38. Sullivan MW, Talamonti MS, Sithanandam K, et al. Results of gastric interposition for reconstruction of the pharyngoesophagus. *Surgery.* 1999;126:666- 672.

39. Pingree TF, Davis RK, Reichman O, Derrick L. Treatment of hypopharyngeal carcinoma: a 10-year review of 1362 cases. *Laryngoscope.* 1987;97:901-904.

40. Ho CM, Lam KH, Wei WI, et al. Squamous cell carcinoma of the hypopharynx: analysis of treatment results. *Head Neck.* 1993;15:405-412.

41. Persky MS, Daly JR. Combined therapy versus curative radiation in the treatment of pyriform sinus carcinoma. *Otolaryngol Head Neck Surg.* 1981;89:87-91.

42. Spiro RH, Bains MS, Shah JP, Strong EW. Gastric transposition for head and neck cancer: a critical update. *Am J Surg*. 1991;162:348-351.

43. Axon PR, Woolford TJ, Hargreaves SP, et al. A comparison of surgery and radiotherapy in the management of post-cricoid carcinoma. *Clin Otolaryngol.* 1997; 22:370-374.

44. Mendenhall W, Parsons J, Devine J. Squamous cell carcinoma of the pyriform sinus treated with surgery and/or radiotherapy. *Head Neck Surg.* 1987;10:88-93

45. Lam KH, Wong J, Lim ST, Ong GB. Pharyngogastric anastomosis following pharyngolaryngoesophagectomy: analysis of 157 cases. *World J Surg*. 1991;5:509-516.

46. Spiro RH, Shah JP, Strong EW, Gerold FP, Bains MS. Gastric transposition in head and neck surgery: indications, complications and expectations. *Am J Surg.* 1983;146:483-487.

47. Harrison DF, Thompson AE. Pharyngolaryngoesophagectomy with pharyngogastric anastomosis for cancer of the hypopharynx: review of 101 operations. *Head Neck Surg.* 1986;8:418-428.

48. Azurin DJ, Go LS, Kirkland ML. Palliative gastric transposition following pharyngolaryngoesophagectomy. *Am Surg.* 1997;63:410-413

49. Ong GB, Lee TC. Pharyngogastric anastomosis after esophageal pharyngectomy for carcinoma of the hypopharynx and cervical esophagus. Br J Surg. 1960;45:193–200.

50. Wight RG, Birchall MA, Stafford ND, Stanbridge RL. Management of hypopharyngeal carcinoma: a 6-year review. J R Soc Med. 1992 Sep;85(9):545-547.

51.Marmuse JP, Koka VN, Guedon C, Benhan G. Surgical treatment of carcinoma of the proximal esophagus. Am Surg. 1995; 169: 386–390.

52. Stell PM, Misotten F, Singh SD, Ramadan MF, Morton RP. Mortality after surgery for

hypopharyngeal cancer. Br J Surg. 1983; 70:713-718.

53. Bottger T, Bumb P, Dutkowski P, Schlick T, Junginger T. Carcinoma of the hypopharynx and the cervical oesophagus: a surgical challenge. Eur J Surg. 1999;165(10):940-946.

54. Cole CJ, Garden AS, Frankenthaler RA, et al. Postoperative radiation of free jejunal autografts in patients with advanced cancer of the head and neck. Cancer. 1995; 75: 9–13.

55. Bardini R, Ruol A, Peracchia A. Therapeutic options for cancer of the hypopharynx and cervical oesophagus. *Ann Chir Gynaecol.* 1995;84:202-207.

56. Jean-Pierre Triboulet, MD; Ch Surgical Management of Carcinoma of the Hypopharynx and Cervical Esophagus Analysis of 209 Cases ristophe Mariette, MD; *MD ARCH SURG/VOL 136, OCT 2001* .

57. Hartley BE, Bottrill ID, Howard DJ. A third decade's experience with the gastric pull-up operation for hypopharyngeal carcinoma: changing patterns of use. J Laryngol Otol.1999 Mar; 113(3):241-243

58. J. Rezaie1, H. Peyvandi2 GASTRIC PULL-UP RECONSTRUCTION FOR PHARYNGOLARYNGOESOPHAGECTOMY IN HEAD AND NECK CANCER AND CERVICAL ESOPHAGEAL, *Acta Medica Iranica*, 45(6): 473-476; 2007.

59. Eckel HE, Staar S, Volling P, Sittel C, Damm M, Junghuelsing M. Surgical treatment for hypopharyngeal carcinoma, feasibility, mortality, and results. Otolaryngology Head Neck Surg 2001: 124: 561-9.

60. Godballe C, Jorgensen K, Hansen O, Bastholt L. Hypopharyngeal cancer: results of treatment based on radiation therapy and salvage surgery. Laryngoscope 2002: 112:834-8.

61. Stoeckli SJ, Pawlick AB, Lipp M, Huber A, Schmid S. Salvage surgery after failure of nonsurgical therapy for carcinoma of the larynx and hypopharynx. Arch Otolaryngology Head and Neck Surg 2000: 126:1473-7.

62. Kean TJ, Hawkins NV, Beale FA, Cummings BJ, Harwood AR, Payne DG, et al. Carcinoma of the hypopharynx: results of primary radical radiation therapy. Int J Radiation Oncol Biol Phys 1983: 9:59-64.

63. Department of Veterans Affairs Laryngeal Cancer Cooperative Study Group. Induction chemotherapy plus radiation compared with surgery plus radiation in patients with advanced laryngeal cancer. N Engl J Med 1991;324:1685-90

64. Lefebvre JL, Chevalier D, Luboinsky B, Kirkpatrick A, Collette L, Sahmoud T. Larynx preservation in pyriform sinus cancer: preliminary results of a European Organization for Research and Treatment of Cancer phase III trial. EORTC Head and Neck Cancer Cooperative Group. J Natl Cancer Inst 1996:88:890-9.

65. Jacobs JR, Weaver A, Ahmed K, et al. Proto –chemo-therapy in advanced Head and Neck cancer. Head Neck 10:93:1987.

66. Hill BT, Price LA, McRae K: Importance of primary site in assessing chemotherapy response and 7-year survival data in advanced squamous cell carcinomas of Head and neck treated with initial combination chemotherapy with cisplatin. J Clinc Oncol 4:1340, 1986.

67. Hitt R, Lopez- pousa A, Martinez-Trufero J, et al. Phase III study of comparing cisplatin plus 5-FU to paclitaxel, cisplatin, and 5-FU induction chemotherapy followed by chemoradiotherapy in locally advanced Head and Neck cancer. J Clin Oncol. 2005;23:8636-8645.

68. Vermorken JB, Remenar E, Van Herpen C, et al. Standard cisplatin/infusional 5-FU (PF) Vs Docetaxel (T) plus PF (TPF) as neoadjuvant chemotherapy for nonresectable locally advanced squamous cell carcinoma of Head and Neck (LA-SCCHN) : a phase III trial of the EORTC Head and Neck Cancer group (EORTC#24971), Proc Am Soc Clin Oncol, 2004;23:5508.

69. Mendelsohn J, Baselga J. Status of epidermal growth factor receptor antagonists in the biology and treatment of cancer. J Clin Oncol 2003;21:2787-99.

70. Hynes NE, Lane HA. ERBB receptors and cancer: the complexity of targeted inhibitors. Nat Rev Cancer 2005;5:341-54. [Erratum, Nat Rev Cancer 2005;5:580.]

71. Dassonville O, Formento JL, Francoual M, et al. Expression of epidermal growth factor receptor and survival in upper aerodigestive tract cancer. J Clin Oncol 1993;11:1873-8.

72. Rubin Grandis J, Melhem MF, Gooding WE, et al. Levels of TGF-alpha and EGFR protein in head and neck squamous cell carcinoma and patient survival. J Natl Cancer Inst 1998;90:824-32.

73. Ang KK, Andratschke NH, Milas L. Epidermal growth factor receptor and response of head-and-neck carcinoma to therapy. Int J Radiat Oncol Biol Phys 2004; 58:959-65.

74. Eriksen JG, Steiniche T, Askaa J, Alsner J, Overgaard J. The prognostic value of epidermal growth factor receptor is related to tumor differentiation and the overall treatment time of radiotherapy in squamous cell carcinomas of the head and neck. Int J Radiat Oncol Biol Phys 2004;58:561-6.

75. Ang KK, Berkey BA, Tu X, et al. Impact of epidermal growth factor receptor expression on survival and pattern of relapse in patients with advanced head and neck

carcinoma. Cancer Res 2002;62:7350-6.

76. Gupta AK, McKenna WG, Weber CN, et al. Local recurrence in head and neck cancer: relationship to radiation resistance and signal transduction. Clin Cancer Res 2002;8:885-92.

77. Liang K, Ang KK, Milas L, Hunter N, Fan Z. The epidermal growth factor receptor mediates radioresistance. Int J Radiat Oncol Biol Phys 2003;57:246-54. Bonner JA, Maihle NJ, Folven BR, Christianson TJ, Spain K. The interaction of epidermal growth factor and radiation in human head and neck squamous cell carcinoma cell lines with vastly different radiosensitivities. Int J Radiat Oncol Biol Phys 1994;29:243-7.

78. Saleh MN, Raisch KP, Stackhouse MA, et al. Combined modality therapy of A431 human epidermoid cancer using anti-EGFr antibody C225 and radiation. Cancer Biother Radiopharm 1999;14:451-63.

79. Huang SM, Bock JM, Harari PM. Epidermal growth factor receptor blockade with C225 modulates proliferation, apoptosis, and radiosensitivity in squamous cell carcinomas of the head and neck. Cancer Res 1999;59:1935-40.

80. Saleh MN, Raisch KP, Stackhouse MA, et al. Combined modality therapy of A431 human epidermoid cancer using anti-EGFr antibody C225 and radiation. Cancer Biother Radiopharm 1999;14:451-63.

81. Huang SM, Bock JM, Harari PM. Epidermal growth factor receptor blockade with C225 modulates proliferation, apoptosis, and radiosensitivity in squamous cell carcinomas of the head and neck. Cancer Res 1999;59:1935-40.

82. Huang S, Harari PM. Modulation of radiation response following EGFR blockade in squamous cell carcinomas: inhibition of damage repair, cell cycle kinetics and tumor

angiogenesis. Clin Cancer Res 2000;6:2166-74.

83. Milas L, Mason K, Hunter N, et al. In vivo enhancement of tumor radioresponse by C225 antiepidermal growth factor receptor antibody. Clin Cancer Res 2000;6:701-8.

84. Harari PM, Huang SM. Head and neck cancer as a clinical model for molecular targeting of therapy: combining EGFR blockade with radiation. Int J Radiat Oncol Biol Phys 2001;49:427-33.

85. Robert F, Ezekiel MP, Spencer SA, et al. Phase I study of anti-epidermal growth factor receptor antibody cetuximab in combination with radiation therapy in patients with advanced head and neck cancer. J Clin Oncol 2001;19:3234-43.

86. Baselga J, Trigo JM, Bourhis J, et al. Phase II multicenter study of the antiepidermal growth factor receptor monoclonal antibody cetuximab in combination with platinum-based chemotherapy in patients with platinum-refractory Metastatic and/or recurrent squamous cell carcinoma of the head and neck. J Clin Oncol 2005;23:5568-77.

87. Herbst RS, Arquette M, Shin DM, et al. Phase II multicenter study of the epidermal growth factor receptor antibody cetuximab and cisplatin for recurrent and refractory squamous cell carcinoma of the head and neck. J Clin Oncol 2005;23: 5578-87.

88. James A. Bonner, M.D., Paul M. Harari, M.D., Jordi Giralt, M.D., Radiotherapy plus Cetuximab for Squamous- Cell Carcinoma of the Head and Neck, N Engl J Med 2006;354:567-78.

89. Fein DA, Mendenhall WM, Parsons JP, Stringer SP, Cassisi NJ, Million RR, Pharyngeal wall carcinoma treated with radiotherapy: impact of treatment technique and fractionation. Int J Radiat Oncol Biol Phys 1993;26:751-7

90. **McKaig RG**, **Baric RS**, **Olshan AF**. Human papillomavirus and head and neck cancer: epidemiology and molecular biology. Head Neck. 1998 May;20(3):250-65

91. Maura L Gillison, Human Papilloma virus- Associated Head and Neck Cancer is distinct Epidemiology, Clinical, and molecular Entity. Seminar in Oncology, 2004;VOL31,No6,744-754